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ULTRARAD

for New Efficiency in chest radiography

(A) Instead of handling cumbersome cassettes individually, load a magazine containing up to 75 non-interleaved 14 x 17 inch films in the Ultrarad.

(B) Easy as 1, 2, 3: 1. Position patient (standing, seated or recumbent). 2. Adjust unit and x-ray tube with hand control to accommodate patient's height. 3. Insert ID card — presto! — you are ready for exposure.

There are other Ultrarad features too — quick access to screens and transport area for cleaning — spare magazines furnished — snap-on cassette holder and grid — adaptable to photo-timing. For details, call your x-ray equipment supplier or write for literature.

- **Fast**
- **Dependable**
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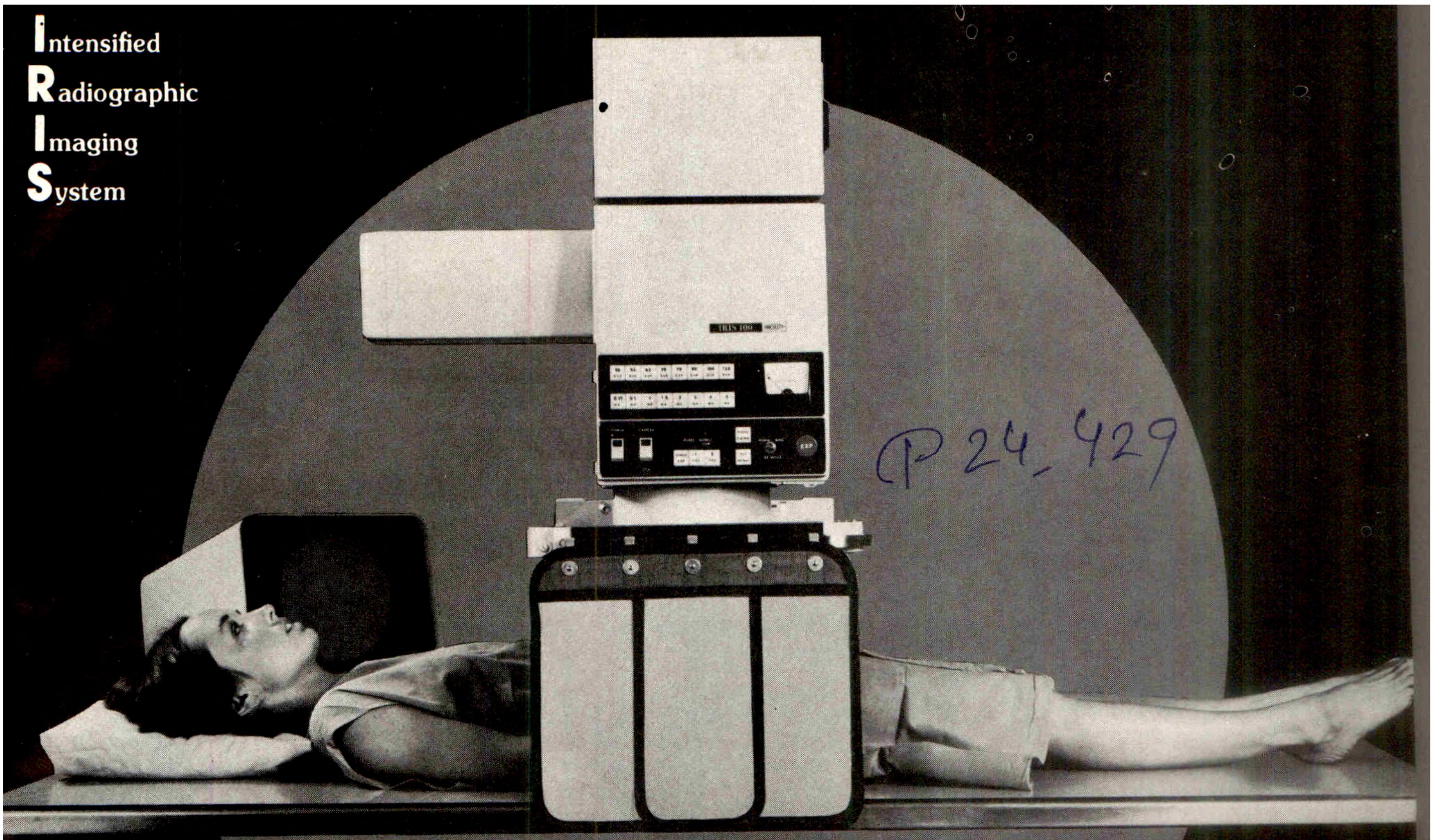
Intensified
Radiographic
Imaging
System



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IRIS 100 adds television fluoroscopy and 100mm spotfilming to your present x-ray room.

Machlett's IRIS 100 system is a sound investment — both for the diagnostician and for the hospital — because it provides the most modern television fluoroscopy/spotfilming capabilities without the need for buying a whole new x-ray room. By improving the radiologist's productivity, moreover, IRIS 100 enables him to apply his much needed skills to a greater patient load.

While its cost is attractive, the real reasons for selecting IRIS 100 for your x-ray room are far more important:

Image Sharpness Machlett's Cesium Iodide Image Intensifier tube with its three focusing grids assures bright, sharp images both on film and on the television screen.

Short F-R-F Time Machlett's "sliding mirror" image distributor lets you quietly shift from fluoroscopy to spot radiography and back to fluoroscopy in *less than one second*.

Rapid Filming The Old Delft "Anodica" camera takes 100mm films singly or sequentially at 1-per-second or 2-per-second rates. Exposures are short enough to freeze peristaltic motion. Phototiming assures uniform film densities.

Human-Engineered Controls Controls are conveniently placed and designed for operation with gloved hands. Warning lights and interlocks eliminate such human errors as exposure without film.

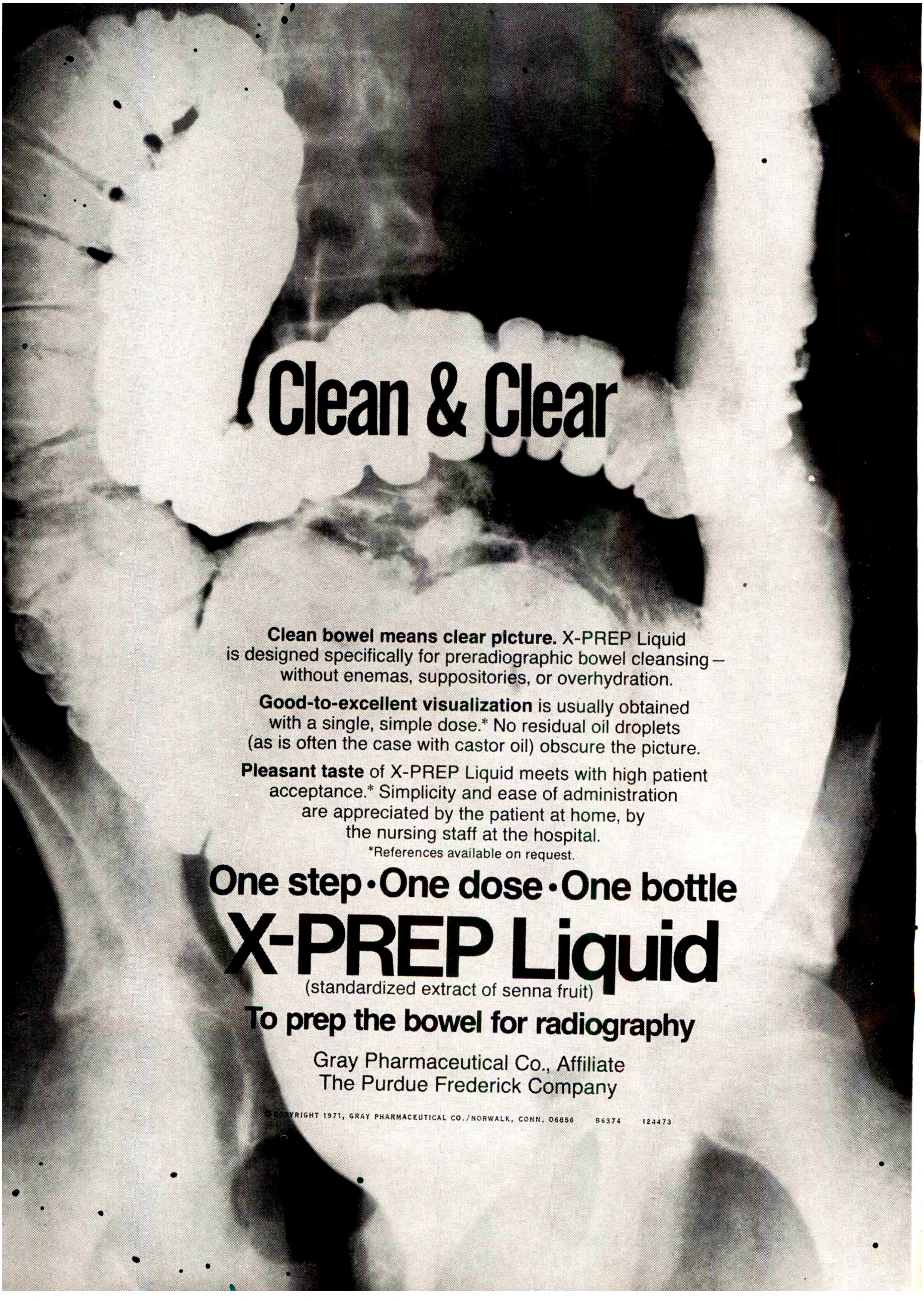
Positive Patient ID The 100mm camera will not operate without the patient identification card in place. Film is identified at the time it is exposed.

For the whole story on IRIS 100, contact your x-ray equipment dealer or

MACHLETT

Machlett Laboratories, Incorporated
A Raytheon Company
1063 Hope Street
Stamford, Connecticut 06907
(203) 348-7511

See the IRIS 100 in Machlett's booth at the RSNA Meeting.



Clean & Clear

Clean bowel means clear picture. X-PREP Liquid is designed specifically for preradiographic bowel cleansing – without enemas, suppositories, or overhydration.

Good-to-excellent visualization is usually obtained with a single, simple dose.* No residual oil droplets (as is often the case with castor oil) obscure the picture.

Pleasant taste of X-PREP Liquid meets with high patient acceptance.* Simplicity and ease of administration are appreciated by the patient at home, by the nursing staff at the hospital.

*References available on request.

One step • One dose • One bottle

X-PREP Liquid

(standardized extract of senna fruit)

To prep the bowel for radiography

Gray Pharmaceutical Co., Affiliate
The Purdue Frederick Company

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Figures should be submitted as 5″×7″ glossy prints, untrimmed and unmounted. Identifying information (authors, title, figure number and indication of the top of the figure) should be attached to the back of each figure with a gummed label. Line illustrations and graphs should be drawn in black ink on white background. Labels on all figures should be of professional quality and size to be easily read when reduced in size.

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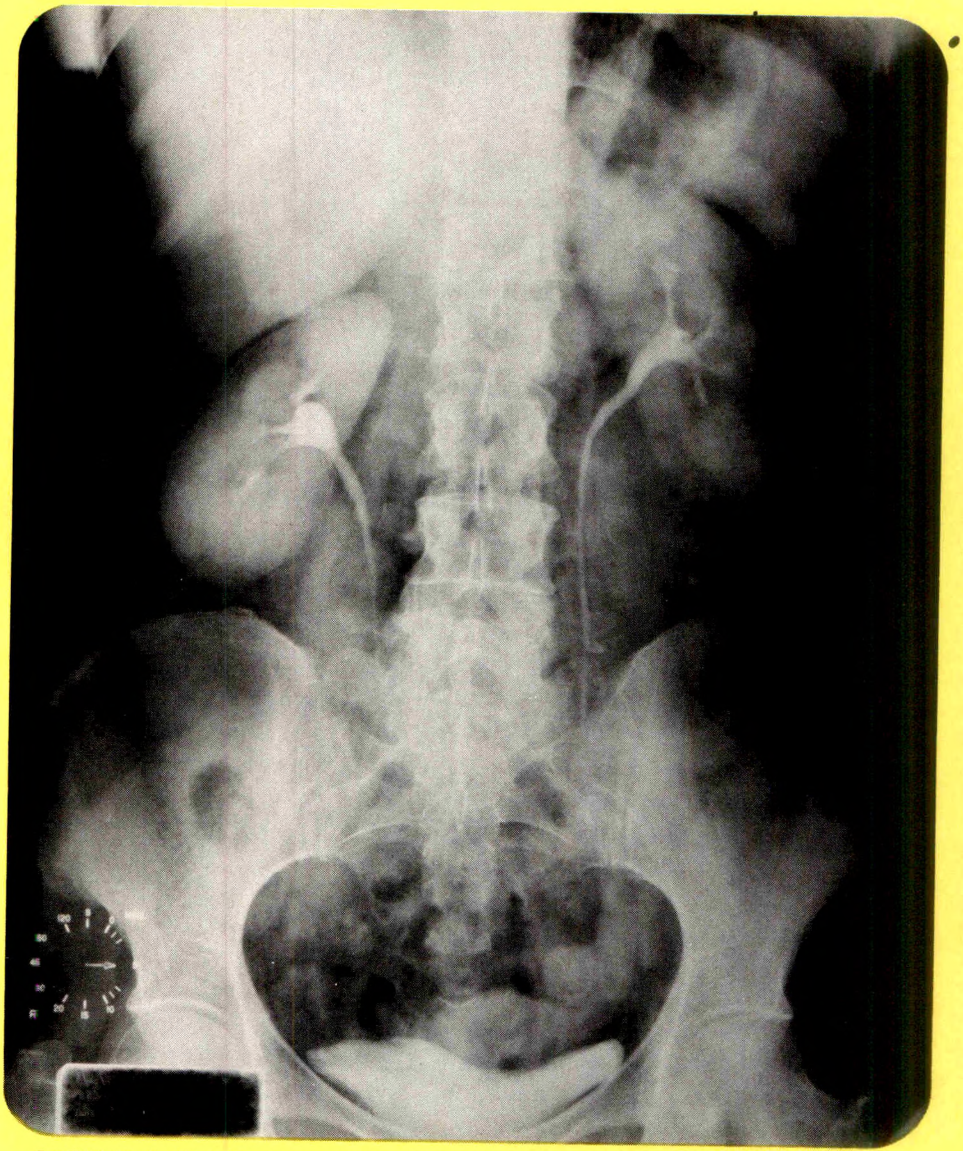

Excellent visualization in intravenous pyelogram 18 hours after administration of 2½ oz. X-PREP Liquid for preradiographic bowel cleansing. (In the files of the Medical Department of The Purdue Frederick Company.)

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☐ X-PREP Liquid is designed specifically for preradiographic bowel cleansing — without enemas, suppositories or overhydration.

☐ A single 2½ oz. oral dose is usually all that is required. No residual oil droplets (such as may occur with castor oil).

☐ Pleasant taste meets with high patient acceptance. Ease of administration is appreciated by the patient and nursing staff.

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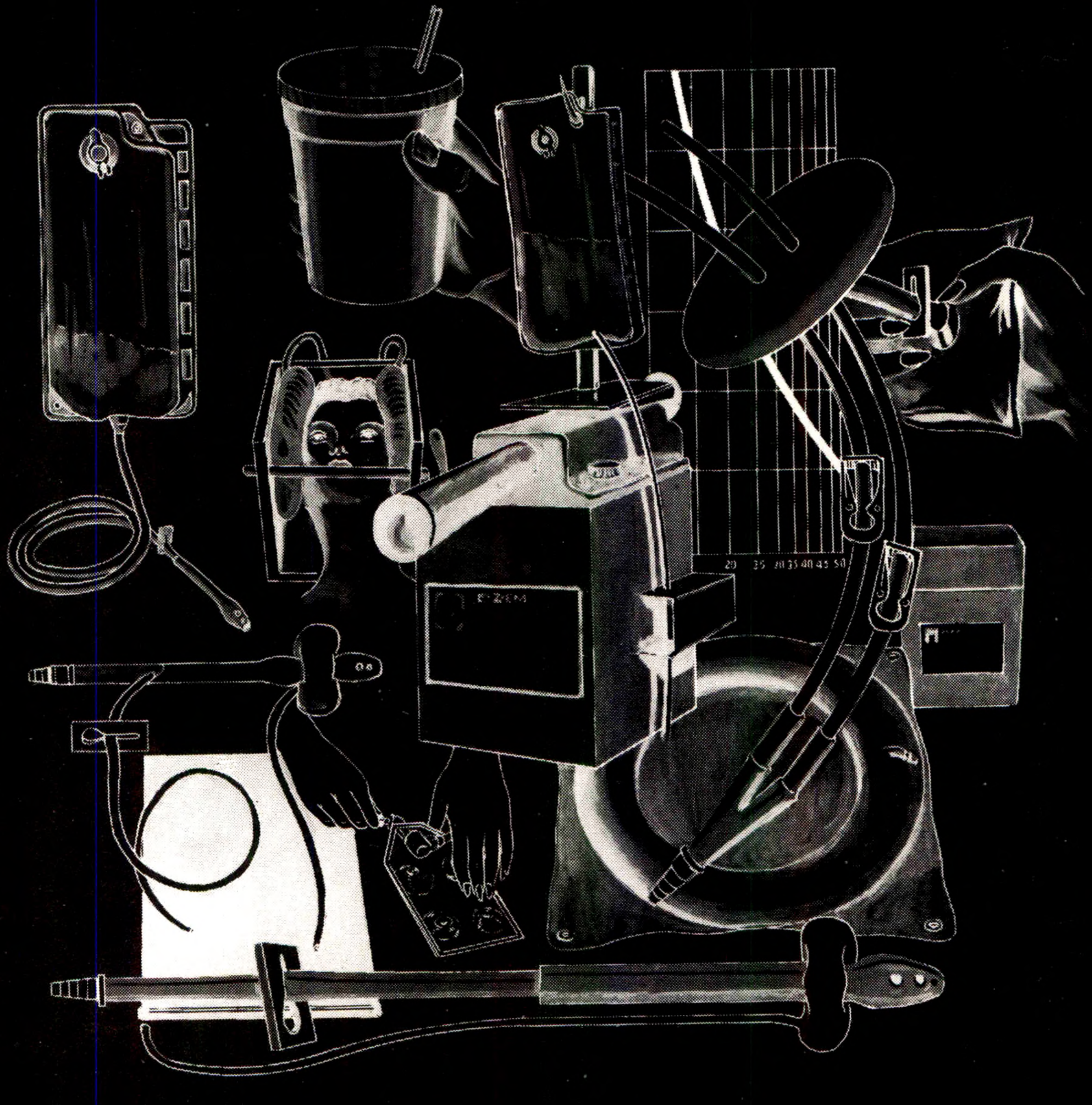

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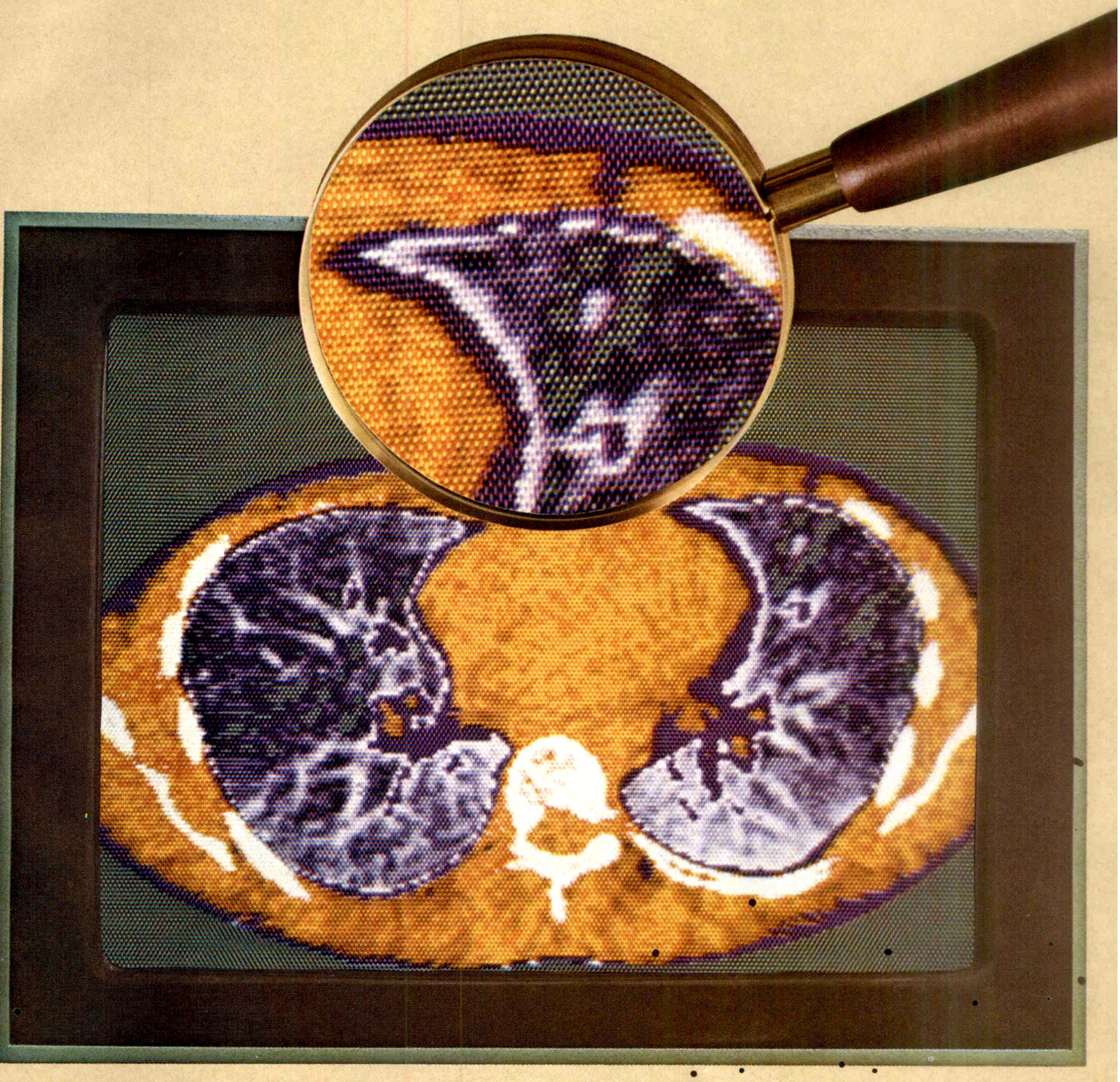

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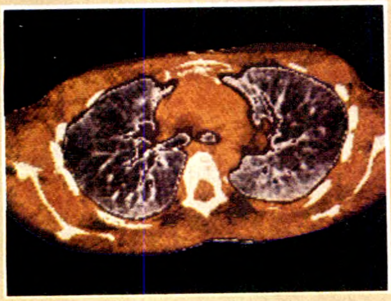
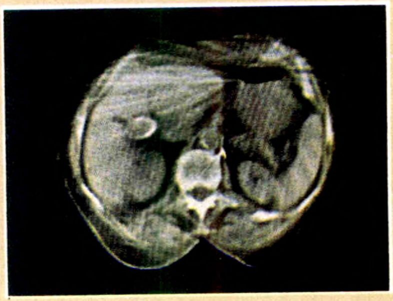
This means a large, high-resolution display (1.5 mm) with greater clarity and true detail—important in extracranial scanning.



Thoracic 320 Scan. (Normal Chest)

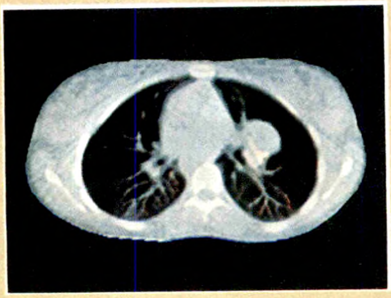


Abdominal 320 Scan. "Porcelain" Gallbladder

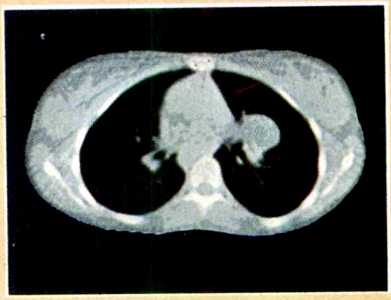
Multiple windows let you see more

With the Pfizer ACTA-Scanner, multiple windows can be imposed upon the image, allowing tissues with great density differences to be viewed at the same time in a single ACTA-scan.

This capability greatly facilitates interpretation of scans in the thoracic and abdominal areas.



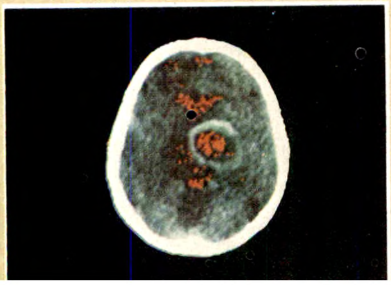
Thoracic scan with multiple windows. Mass in right lung.



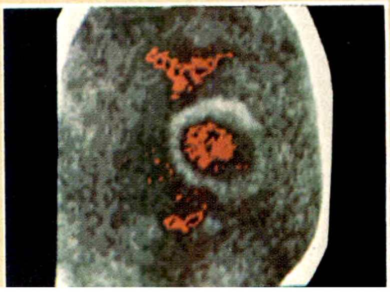
Same area as scanned at left, without imposition of the multiple window capability.

And you can enlarge selected areas

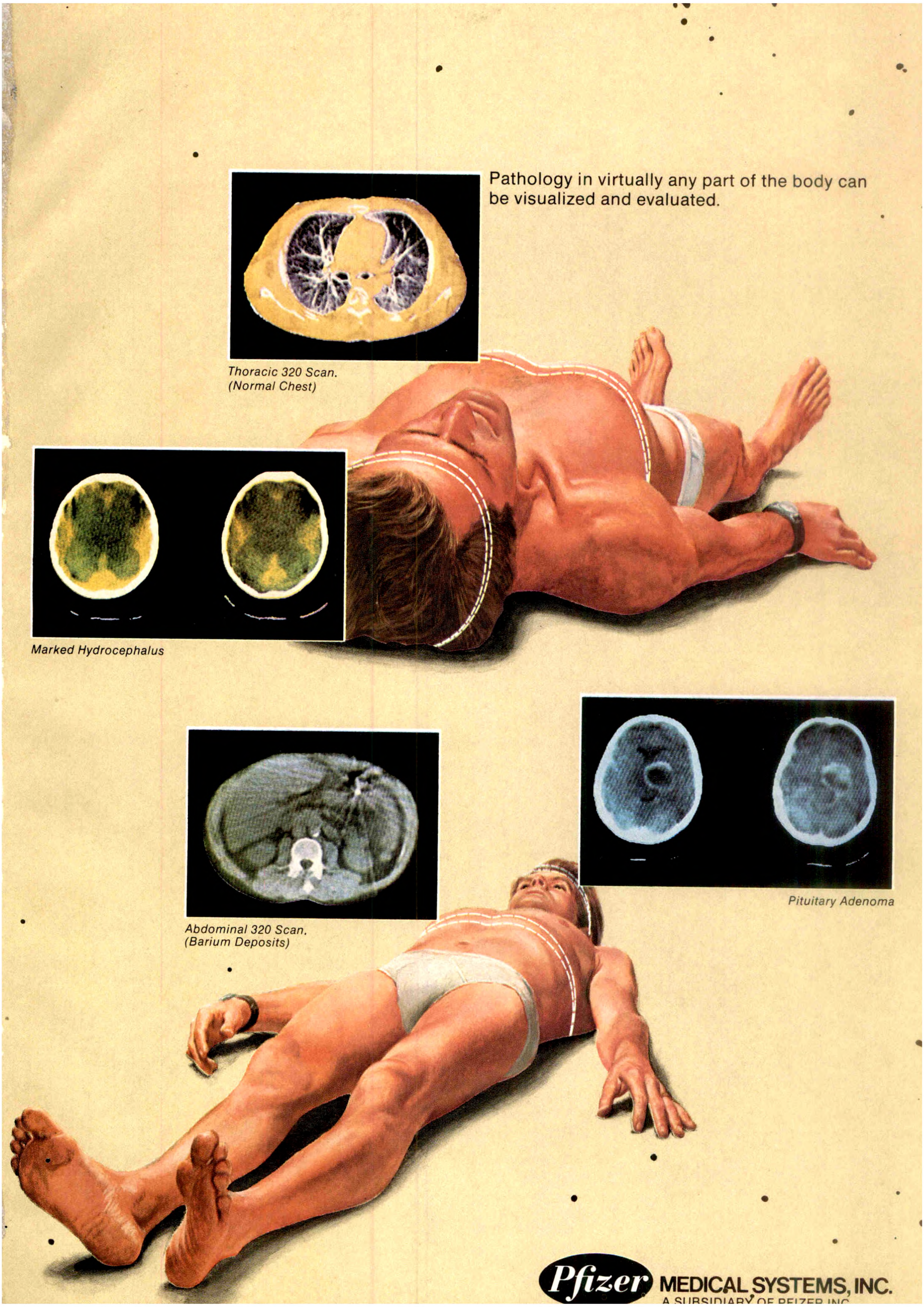
A special cursor—or movable dot—allows the operator of the ACTA-Scanner to enlarge selected areas of interest by a factor of 2 in diameter (4 in area).



Pituitary Adenoma



Pituitary Adenoma. Instantaneous enlargement of pathologic area.



Pathology in virtually any part of the body can be visualized and evaluated.

Thoracic 320 Scan.
(Normal Chest)

Marked Hydrocephalus

Abdominal 320 Scan.
(Barium Deposits)

Pituitary Adenoma

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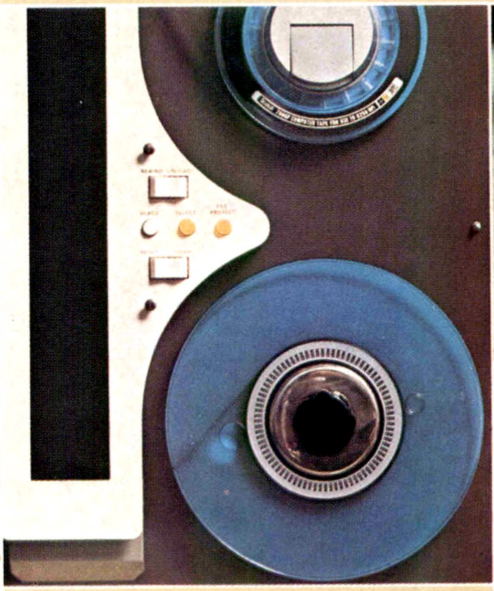
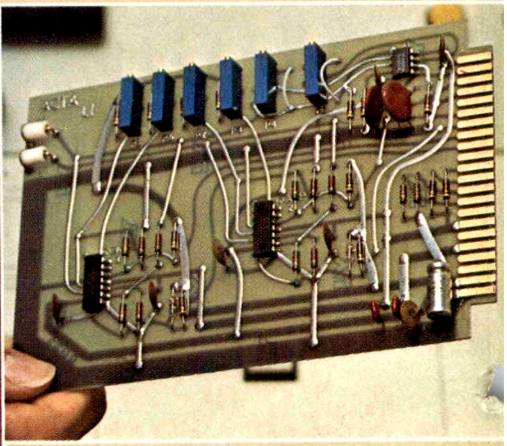
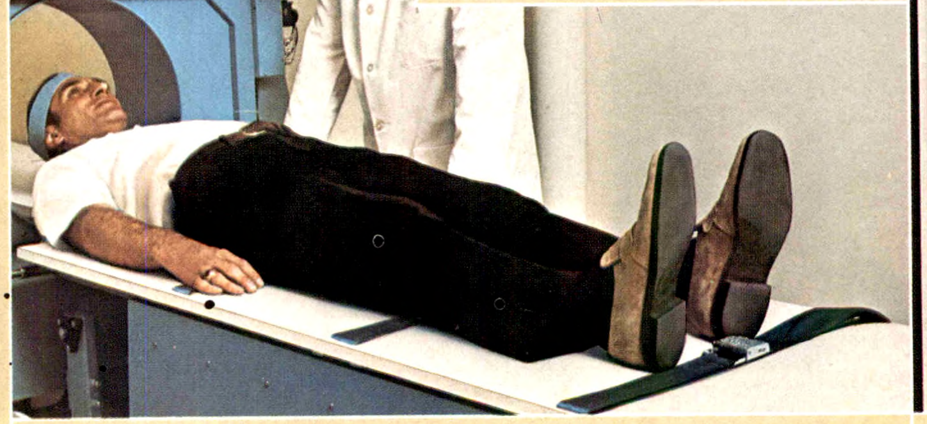


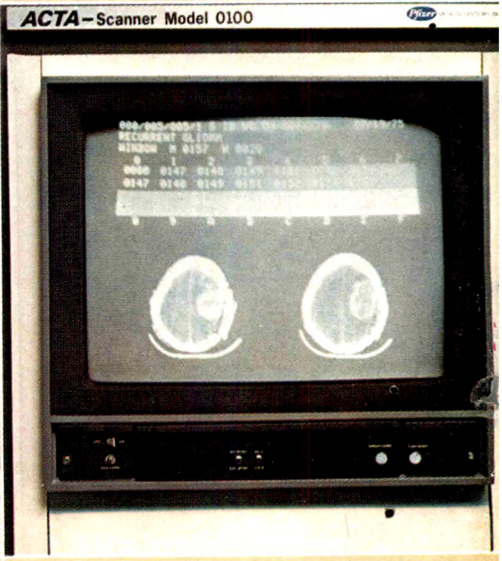
All data stored on magnetic tape for future recall



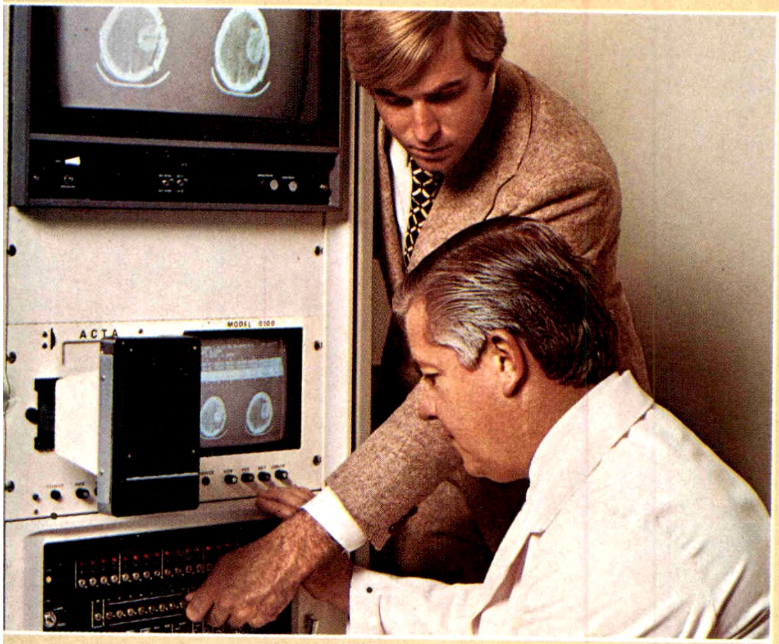
Replacement parts, if needed, are readily available



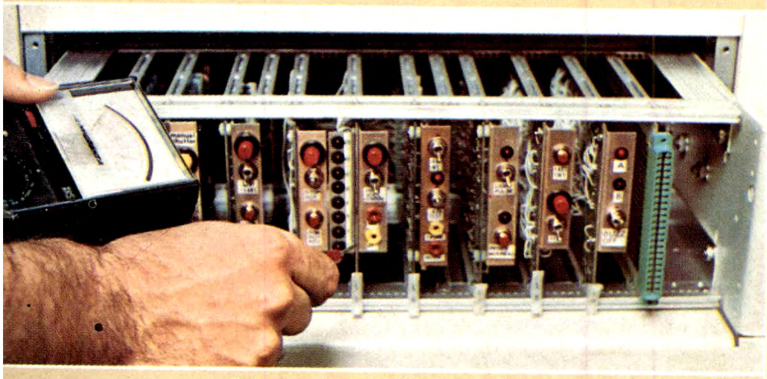
Minimal patient preparation before scan



Instant display following completion of scan



Field engineer provides continued updating on capabilities



Frequent visits by field engineer keep ACTA-Scanner at peak performance

Automation with Representation

A team of highly qualified field engineers is on standby duty to respond to your needs within two hours, if necessary.

Warranty: Any necessary maintenance can be done at night or during nonpeak hours, as designated. No charges for all parts and service support during normal working hours.

Continuous inspection: Frequent visits, at your convenience, will be made to assure optimum performance.

Direct link to research and development: Your representative will keep you apprised of the activities of the Pfizer physicists and x-ray and computer experts who are dedicated to providing ever greater performance and more features on your ACTA-Scanner.

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The Philips Integrated Therapy Programme ensures increased efficiency in the modern radiotherapy department by having a common design philosophy, similarity of operational procedures, and simplified service.

The programme embodies maximum reliability and patient safety. It incorporates a long-term plan providing the clinic and hospital with essential equipment for today and the future.

The SL75 Linear Accelerator.

The SL75/10MeV Linear Accelerator is the result of continuous development and clinical experience over many years. It has now established its leadership world-wide for reliability, accuracy and simplicity.

Further developments based on this experience have now culminated in the addition of two more accelerators to this series: the SL75/20MeV and the SL75/5MeV.

All these units incorporate the highest standards of engineering and patient safety.

The Cobalt 60 unit.

Many radiotherapy departments rely almost entirely on the Cobalt 60 unit, where it is used to its fullest capacity.

The Philips Cobalt 60 unit in its many versions is the optimum unit for rapid and accurate therapy at low capital cost and with the minimum of maintenance.

The Treatment Planning System.

Although computer-aided treatment planning is now almost universally adopted by the radiotherapy clinic, there is still an urgent need for a rapid, dedicated and interactive system to permit the therapist to compile and modify plans rapidly and accurately. Such a system demands a conventional and familiar method requiring no specialised computer knowledge.

This need has been met completely by the unique Philips Treatment Planning System which calculates and displays depth dose information for fixed and moving beams on a three-dimensional basis. A hard copy of the final treatment plan is processed in a matter of seconds.

Localiser/Simulator.

As the patient-loads in every radiotherapy clinic increase, it becomes necessary to do as much preparation as possible outside the treatment room.

The Philips Simulator rapidly and accurately checks the proposed treatment plans produced for the Cobalt 60 unit, linear accelerators or betatron, improving the overall efficiency of the therapy department.

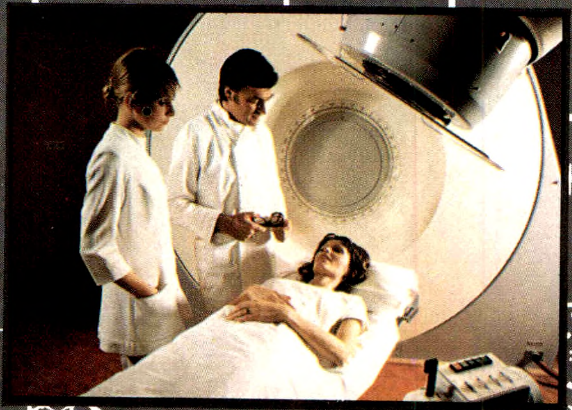
Ortho-Voltage Radiotherapy Equipment.

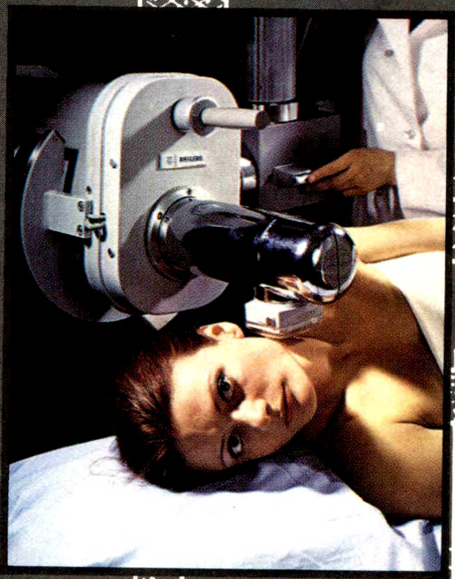
In any radiotherapy clinic, ortho-voltage radiotherapy equipment fills an important role. The Philips integrated radiotherapy programme includes units ranging from 50kV contact therapy equipment to a 300kV fixed voltage, constant dose rate unit, providing alternative treatment for contact, intermediate and deep therapy.

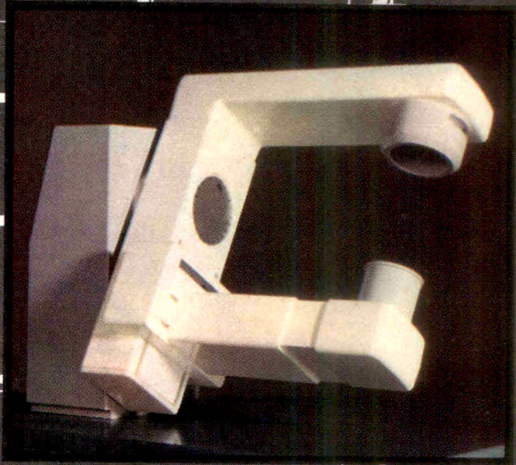
Specialised Equipment.

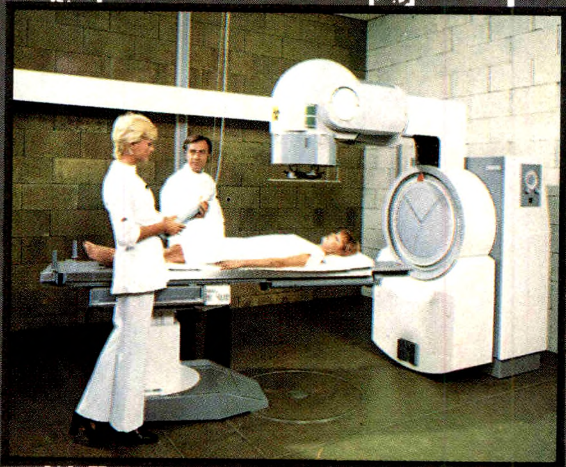
Apart from the megavoltage and ortho-voltage units, the Philips Integrated Therapy Programme includes additional equipment for increased efficiency. The provision of data verification and print-out facilities on mega-voltage units eliminates the possibility of setting errors and reduces the strain on the operator, thereby increasing overall patient safety. In line with the latest interest of the radiotherapist, Philips are now evaluating a Neutron Therapy Unit in clinical use.

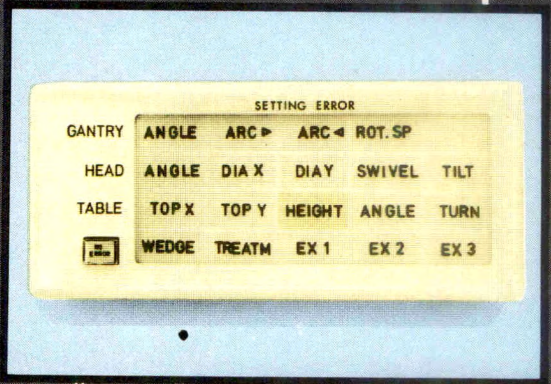
If you would like to know more about the Philips Integrated Therapy Programme,
please write to: N.V. Philips, Medical Systems, Eindhoven, The Netherlands,
or Philips Medical Systems Ltd., The M.E.L. Equipment Company Ltd., Manor Royal, Crawley, Sussex, England.











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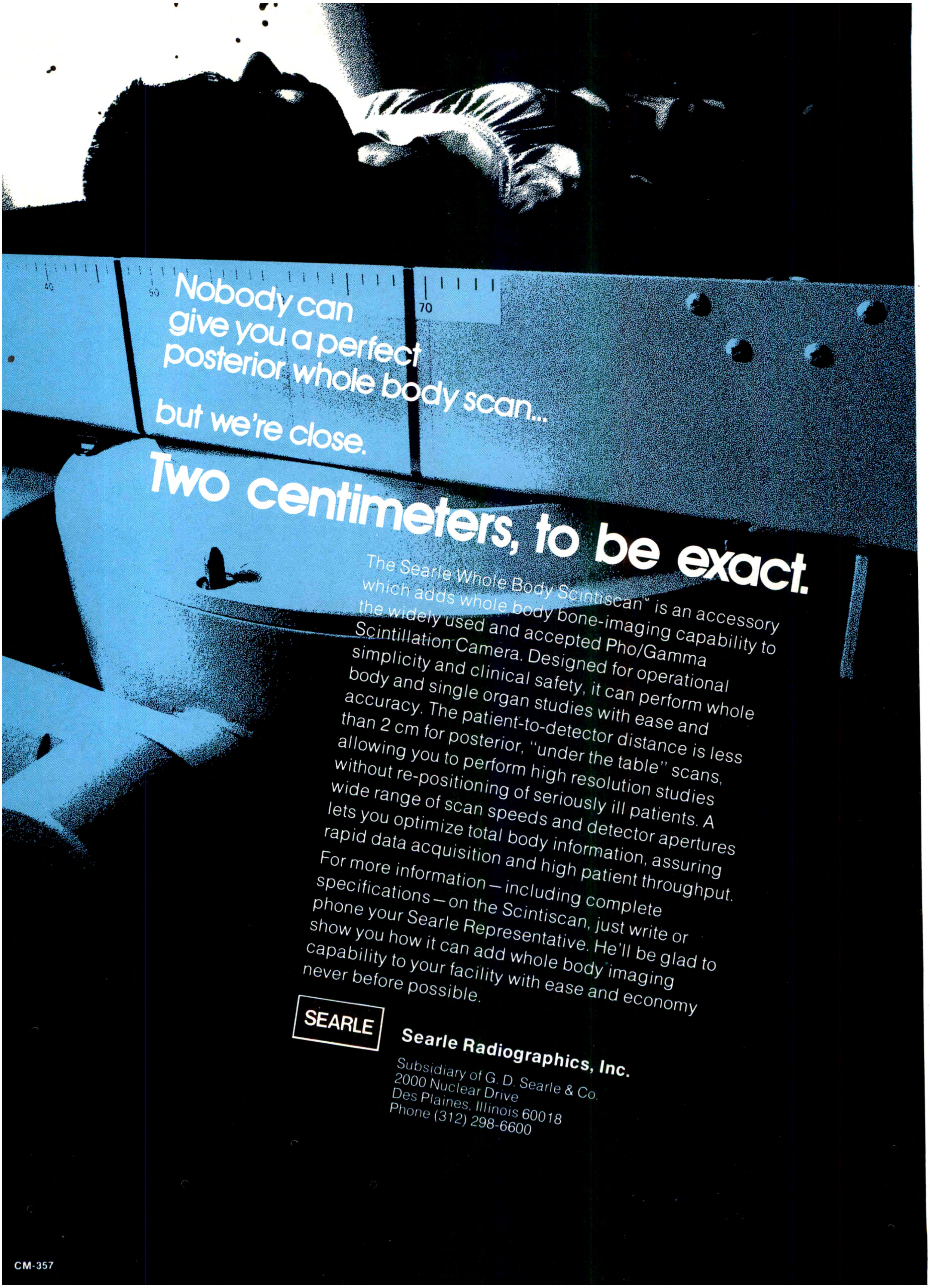

Nobody can give you a perfect posterior whole body scan...

but we're close.

Two centimeters, to be exact.

The Searle Whole Body Scintiscan™ is an accessory which adds whole body bone-imaging capability to the widely used and accepted Pho/Gamma Scintillation Camera. Designed for operational simplicity and clinical safety, it can perform whole body and single organ studies with ease and accuracy. The patient-to-detector distance is less than 2 cm for posterior, "under the table" scans, allowing you to perform high resolution studies without re-positioning of seriously ill patients. A wide range of scan speeds and detector apertures lets you optimize total body information, assuring rapid data acquisition and high patient throughput. For more information—including complete specifications—on the Scintiscan, just write or phone your Searle Representative. He'll be glad to show you how it can add whole body imaging capability to your facility with ease and economy never before possible.

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Static, dynamic & whole body imaging . . . 15 formats, 3 film sizes

The Searle Micro Dot Imager offers Pho/Gamma users a versatile display system for single-organ or whole body imaging using economical X-ray film. Three film sizes and 15 image formats let you choose the exact format best suited for any study. State-of-the-art optics and electronics put as many as 80 images on one film with single-image fidelity. You can even mix static, dynamic and different size images on the same sheet of film. An exclusive, lightweight cassette design speeds and simplifies loading and unloading of film.

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Designed for clinical utility and operational simplicity, the Micro Dot Imager is the most complete display system available for the Pho/Gamma Scintillation Camera. For more information—including complete specifications—just write or phone your Searle representative. He'll be glad to show you how it can add unmatched versatility, convenience and economy to your laboratory's gamma imaging capabilities.

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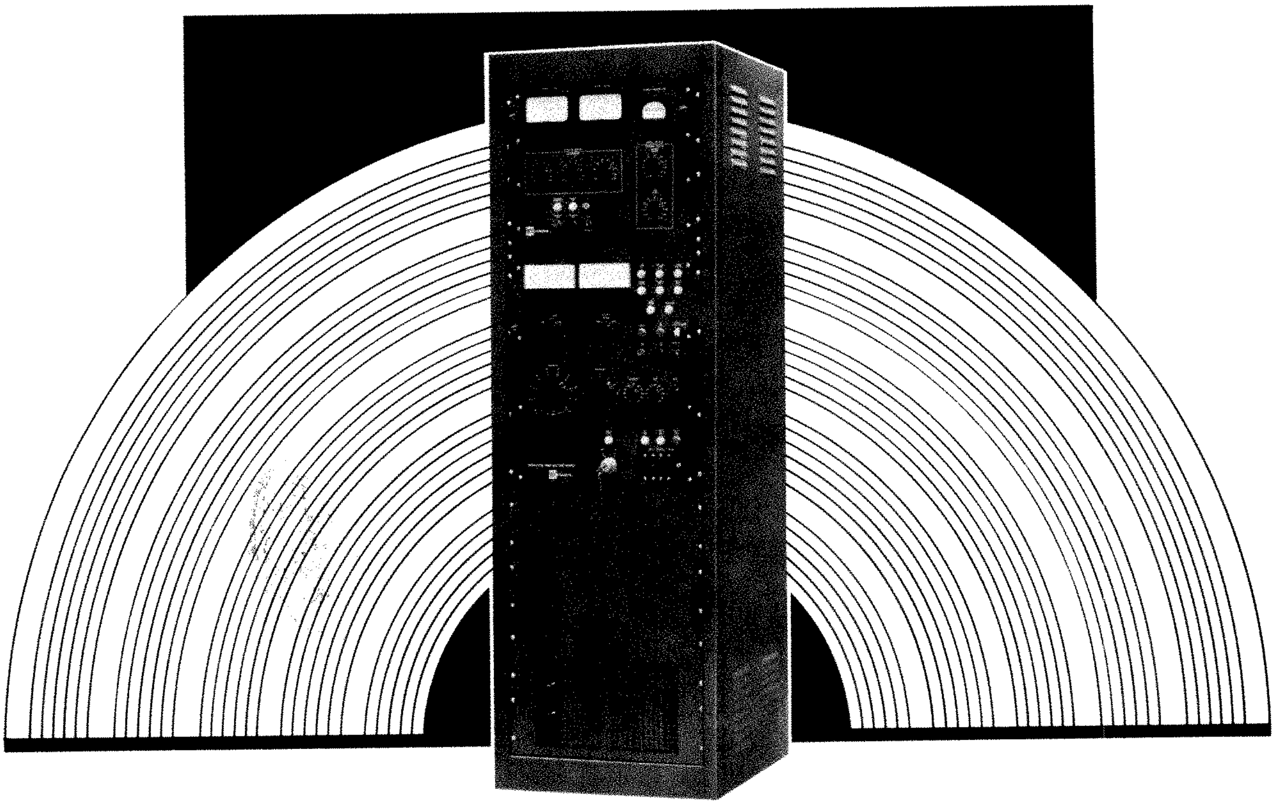
For optimum transverse axial tomographic systems performance

UVC Emission Current Regulators harness x-ray tubes two ways



1. Precisely regulate x-ray voltage
2. Precisely regulate emission current

Compare and evaluate conventional DC power supplies with UVC Emission Current Regulators to fully appreciate the many superior advantages of our equipment.

Here is a unit that precisely and automatically regulates x-ray potential in milliseconds, and provides high stability and repeatability to insure consistent performance.

Small wonder why more and more hospitals are turning to transverse axial tomography systems incorporating UVC Emission Current Regulators for unsurpassed reliability.

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For years, similar UVC equipment has been used by industrial and government laboratories for spectroscopy and diffraction applications. And our experience with power supplies for airport and public building security systems have brought us to the forefront of high voltage reliability and systems compatibility.

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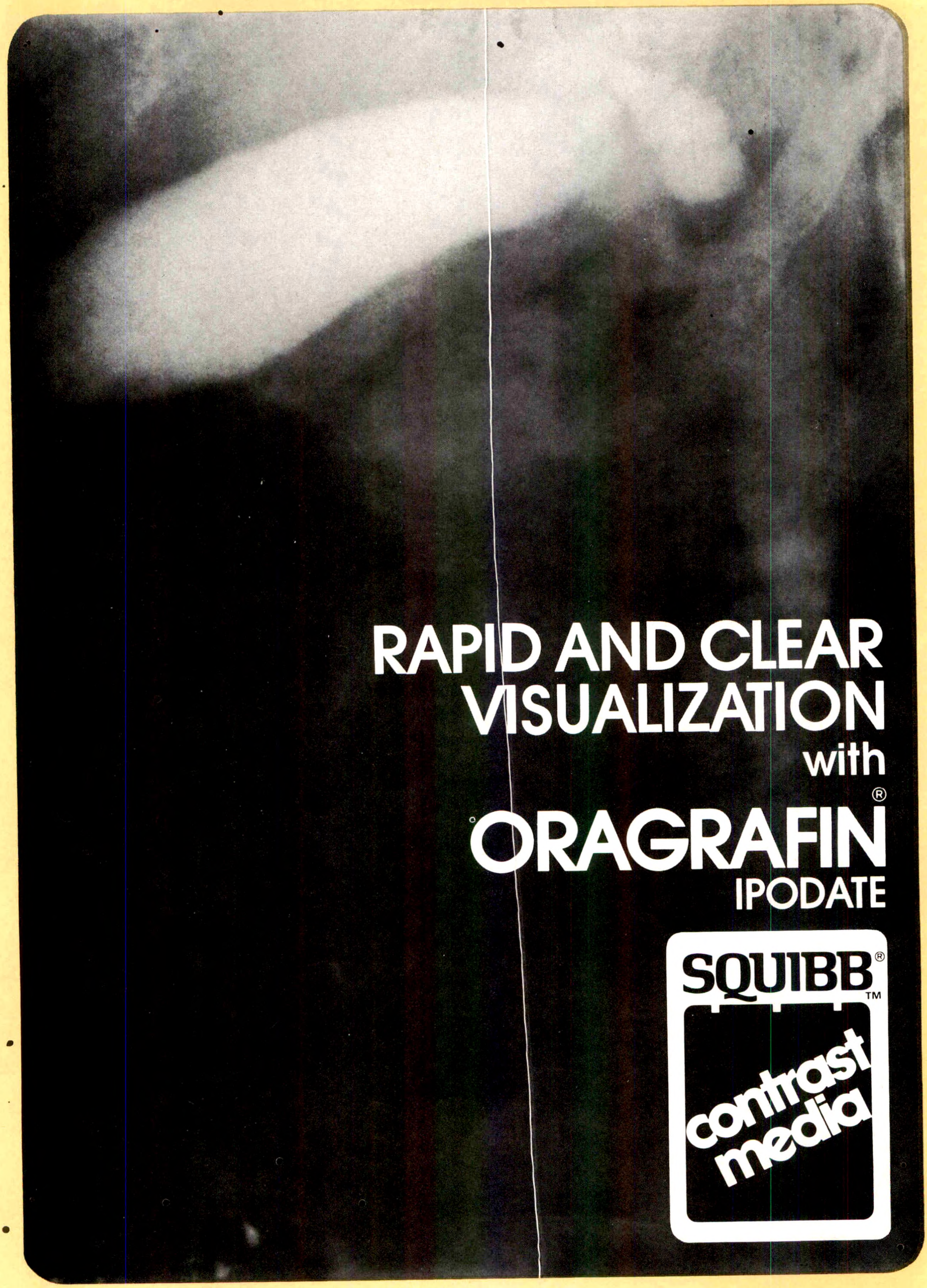

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with
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- Visualization of the ducts occurs in 1 to 3 hours and of the gallbladder within 5 hours or less with Oragrafin Calcium Granules (Calcium Ipodate for Oral Suspension N.F.).
- The gallbladder is opacified approximately 10 hours after ingestion of Oragrafin Sodium Capsules (Sodium Ipodate Capsules N.F.).
- Rapid absorption often permits visualization of even poorly functioning gallbladders. An unprepared patient can be studied the same day.
- When patients cannot take capsules, the granules are a convenient, palatable alternative.
- Both salts are usually well tolerated.

Dosage Schedules

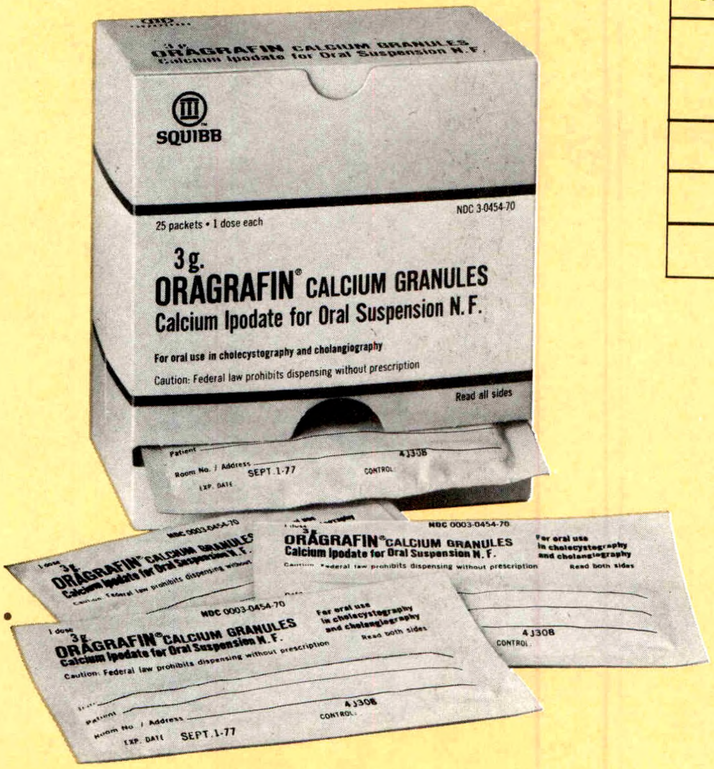
FOR ROUTINE OVERNIGHT PROCEDURES
Sodium Ipodate Capsules and/or Calcium Ipodate for Oral Suspension

	Gallbladder Films			Films of the Gallbladder and Biliary Ducts
11 P.M.	6 Capsules (or 12 Capsules)	OR	1 packet of Granules (or 2 packets)	6 Capsules (or 1 packet of Granules, if preferred) and
next morning, 8 A.M.				1 packet of Granules
9 A.M.	Visualization of gallbladder		Visualization of gallbladder	Visualization of ducts and gallbladder
10 A.M.				
11 A.M.				

FOR RAPID, SAME-DAY PROCEDURES
Calcium Ipodate for Oral Suspension

	Films of Gallbladder and Ductal System
8 A.M.	2 packets of Granules
9 A.M.	Visualization of ducts
10 A.M.	Optimal visualization of ducts
1 P.M.	Visualization of gallbladder

See next page for complete prescribing information.


SQUIBB
25 packets • 1 dose each
NDC 3-0454-70
3 g.
ORAGRAFIN® CALCIUM GRANULES
Calcium Ipodate for Oral Suspension N.F.
For oral use in cholecystography and cholangiography
Caution: Federal law prohibits dispensing without prescription
Read all sides

ORAGRAFIN®
CALCIUM GRANULES
Calcium Ipodate for Oral Suspension N.F.

ORAGRAFIN®
SODIUM CAPSULES
Sodium Ipodate Capsules N.F.

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DESCRIPTION
Oragrafin Calcium Granules (Calcium Ipodate for Oral Suspension N.F.) and Oragrafin Sodium Capsules (Sodium Ipodate Capsules N.F.) are oral radiopaque media for cholangiography and cholecystography. *Calcium* ipodate is available in single-dose foil packets providing 3 g. calcium ipodate as granules dispersed in flavored sucrose. When mixed with water, the granules produce a pleasantly-flavored suspension. *Sodium* ipodate is available in capsules providing 500 mg. sodium ipodate per capsule.

The organically bound iodine content of calcium ipodate and sodium ipodate is 61.7% and 61.4%, respectively.

ACTIONS
Calcium ipodate and sodium ipodate are absorbed from the gastrointestinal tract, excreted by the liver into the bile, and stored and concentrated in the gallbladder. The calcium salt, which is absorbed somewhat faster than the sodium salt, appears in the ducts as early as 30 minutes after ingestion. Optimal concentration of either salt in the hepatic and biliary ducts occurs within 1 to 3 hours after ingestion in nearly all cases; rarely, maximal opacification may be delayed for as much as 5 hours. Adequate opacification of the ducts usually persists for about 45 minutes. The ducts may be visualized in patients who have undergone cholecystectomy.

The gallbladder is optimally opacified approximately 10 hours after ingestion of either salt. Diagnostically adequate filling, however, often takes place within 5 hours or less after ingestion, particularly with the calcium salt. Thus, studies of ducts and gallbladder may be carried out in as little as 5 hours when necessary or desirable. In this connection, it should be pointed out that both salts have been administered to unprepared patients as well as to previously prepared patients, with no significant difference in results.

INDICATIONS
Calcium ipodate and sodium ipodate are indicated for cholecystography. They may also be used for cholangiography, although they are not considered the drugs of choice.

CONTRAINDICATIONS
Both preparations are contraindicated in persons who are hypersensitive to ipodate salts.

WARNINGS
A history of sensitivity to iodine *per se* or to other iodinated compounds is not an absolute contraindication to the use of these preparations, but calls for extreme caution in administration.

Usage in Pregnancy
The safety of these preparations for use during pregnancy has not been established; therefore, they should be used in pregnant patients only when, in the judgment of the physician, their use is deemed essential to the welfare of the patient.

PRECAUTIONS
Increasing the dosage above that recommended increases the possibility of hypotension.

Anuria may result when these preparations are administered to patients with combined renal and hepatic disease or severe renal impairment.

Renal toxicity has been reported in a few patients with liver dysfunction who were given oral cholecystographic agents followed by urographic agents. Administration of urographic agents should therefore be postponed in any patient with a known or suspected hepatic or biliary disorder who has recently taken a cholecystographic contrast agent.

Gastrointestinal disorders which interfere with absorption and liver disorders which interfere with excretion may result in non-visualization of the hepatic and biliary ducts and the gallbladder.

Contrast agents may interfere with some chemical determinations made on urine specimens; therefore, urine should be collected before administration of the contrast media or two or more days afterwards.

Thyroid function tests, if indicated, should be performed prior to the administration of these preparations since iodine containing contrast agents may alter the results of these tests.

ADVERSE REACTIONS
Sodium ipodate and calcium ipodate are usually well tolerated. Unwanted effects such as mild and transient nausea, vomiting, or diarrhea sometimes occur but the incidence can be reduced by restricting the dosage to 3 g. and administering only the Granules to patients who may be prone to gastrointestinal reactions. Headache, dysuria, or abdominal pains may occur infrequently as transient disturbances.

Hypersensitivity reactions may include urticaria, serum sickness-like reactions (fever, rash, arthralgia), other skin rashes, and, rarely, anaphylactoid shock. They are more likely to occur in individuals with a history of allergy, asthma, hay fever, or urticaria, and in those who have previously demonstrated hypersensitivity to iodine compounds.

DOSAGE AND ADMINISTRATION
The Capsules should be taken with as little water as possible. They may be swallowed in rapid succession or slowly over the course of ½ hour or more, depending on patient preference.

The Granules should be stirred vigorously into a small amount of water (¼ glass or less) and swallowed immediately. If lukewarm rather than cold water is used, the patient will find the suspension quite palatable and there will be less likelihood of nausea.

A total dose of 6 g. (12 Capsules or 2 packets of Granules) per 24 hour period should not be exceeded.

When an upper gastrointestinal barium study is scheduled, prior administration of either salt will not interfere. Either salt may also be used in conjunction with an intravenous cholangiographic agent.

The recommended dosage and patient preparation for cholangiography and/or cholecystography are as follows:

Routine Cholecystography
On the day before the examination, the patient may, if feasible, eat a high-fat lunch so that the gallbladder will evacuate and refill with opacified bile. The evening meal, which should be light and fat-free, should be eaten 2 hours before the contrast medium is taken. The contrast agent should be administered 10 to 12 hours before the roentgenologic examination. The usual dose is 6 Capsules (providing 3 g. sodium ipodate), although up to 12 Capsules may be given; 1 to 2 packets of Granules may be used instead. No other food or drink except small amounts of water should be taken before the examination. A mild laxative or other cathartic may be given, but is not generally necessary.

Roentgenologic examination of the gallbladder is performed the next morning in the usual manner, employing the standard positions. An immediate study of the wet films will determine any need for repositioning of the patient. Administration of a fat meal or other cholecystokinetic agent provides good dynamic studies of gallbladder function. If a barium meal examination is also to be performed, the fat meal may be given simultaneously with or following the barium meal. Gallbladder function studies are then made after the barium meal examination is completed.

Cholangiography
No prior preparation of the patient is necessary. For this procedure, the Granules should be used. They are administered one hour before cholangiography. Although only one packet (providing 3 g. calcium ipodate) may suffice, two packets (6 g.) are usually necessary for visualization of the ducts.

Beginning one hour after ingestion of the Granules, and at 15-minute intervals thereafter, films should be taken, preferably with the aid of tomography or laminography. With proper positioning of the patient, residual contrast medium in the gastrointestinal tract is not likely to be a problem, particularly with the more rapidly absorbed calcium salt. Optimal visualization of the ducts is generally achieved between 1½ and 2½ hours after ingestion of the medium.

Combined Cholangiography and Cholecystography
Preparation of the patient and administration of dosage should be as outlined under *Routine Cholecystography*, with a dosage of 6 Capsules or, if preferred, one packet of Granules taken on the evening before examination. On the following morning, one hour before the examination, one additional packet of Granules should be administered.

Beginning one hour after the morning dose, and at 15-minute intervals thereafter, films should be made, preferably with the use of tomography or laminography. While the gallbladder will have concentrated the evening dose of the medium, the additional morning dose will provide opacification of the ducts, and simultaneous visualization may be achieved. When satisfactory films have been obtained, a fat meal may be administered to provide gallbladder function studies.

Rapid Combined Cholangiography and Cholecystography
No prior preparation of the patient is necessary. On the day of examination, the patient should be given two packets of Granules. Beginning one hour later, examination of the ducts should be performed as described under *Cholangiography*. If the gallbladder has not opacified sufficiently by the time the cholangiographic examination is completed, further cholecystograms may be taken after 2 or 3 hours. Dynamic studies of gallbladder function may be carried out in the usual manner.

HOW SUPPLIED
Oragrafin Calcium Granules (Calcium Ipodate for Oral Suspension N.F.), single-dose foil packets; boxes of 25 packets (3 g. calcium ipodate per packet). Oragrafin Sodium Capsules (Sodium Ipodate Capsules N.F.), boxes of 25 vials (6 capsules each vial); bottles of 100; and Unimatic® single-dose packages of 100.

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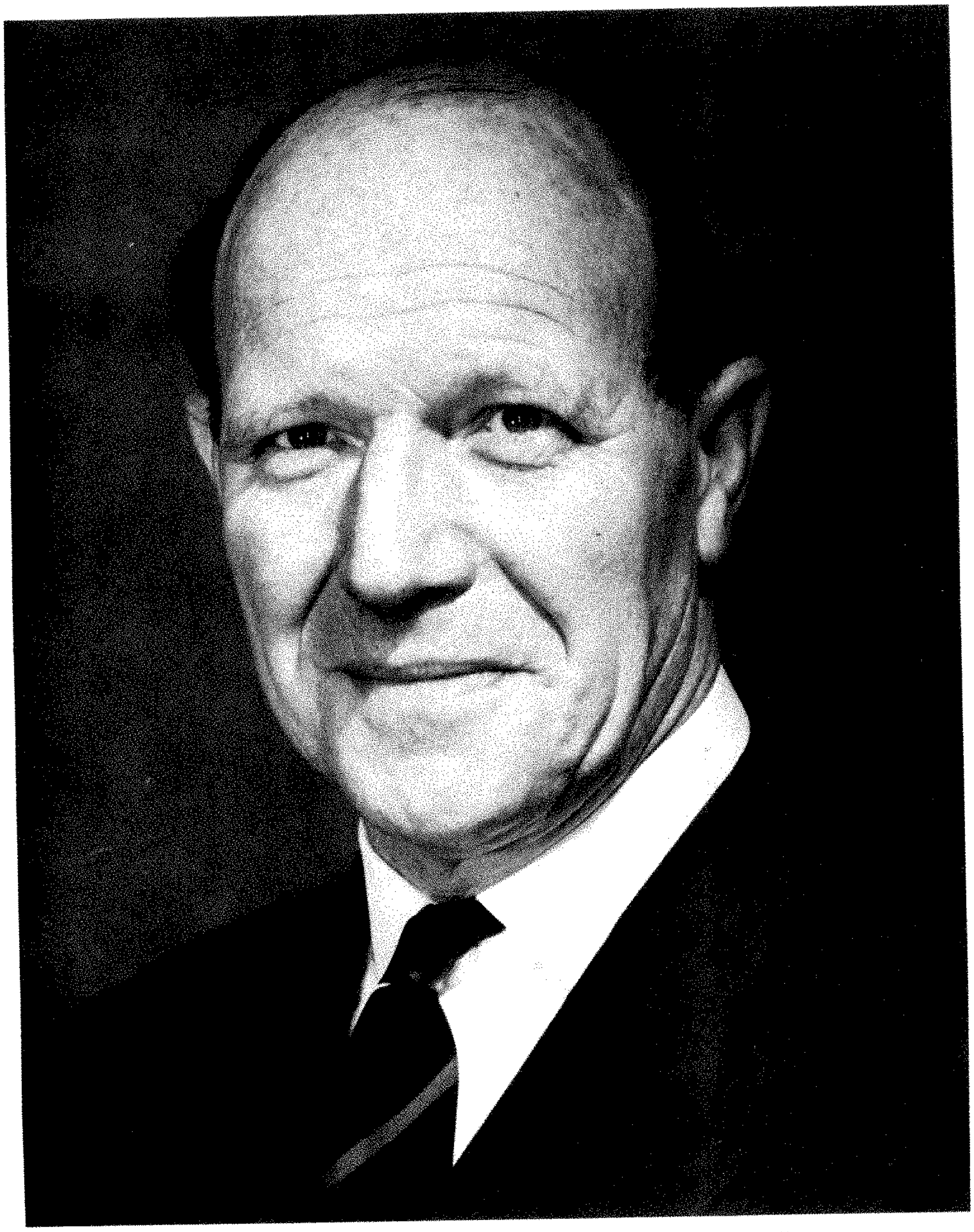

RONALD O. MURRAY, M.B.E., M.D.
CALDWELL LECTURER, 1975

AMERICAN JOURNAL
OF ROENTGENOLOGY

VOL. 126 JANUARY, 1976 NO. 1

INTRODUCTION OF CALDWELL LECTURER, 1975*

By HAROLD G. JACOBSON, M.D.†
BRONX, NEW YORK

The facts reflect a great physician, an inspiring teacher, a scientist of the first magnitude and an indefatigable scholar. These data are, of course, relevant to the occasion. They do not, however, give the full flavor of the real man. It is in a sense, appropriate that Dr. Murray be introduced by an American colleague with whom he has had the closest association—an association which began in 1960 at the Radiological Society of North America meeting in Cincinnati, Ohio, where he was a guest lecturer. This meeting led to further professional contacts from which has evolved gradually a very close and felicitous relationship, which in importance to this speaker, has transcended both on a personal and professional level any other working association.

Your Caldwell Lecturer and the man asked to introduce him have collaborated professionally for almost eight years in a number of endeavors. During this period the qualities which comprise this man have become clearly evident. Dr. Murray's capacity for productive work is unique, having brought him to the pinnacle of his chosen field of skeletal radiology in the entire world. His teaching talents are truly admirable. His mastery of the language of our two countries—both the spoken and written word—is exemplary, and for this speaker who works with him, virtually impossible to emulate.

Of overriding importance, however, to this, his American colleague, is the moral tone, the character and the inner qualities of the real person. His integrity, sense of decency, fairness, empathy for those less fortunate—all are sharply etched against the background of his scientific achievements. He is warm, compassionate and thoroughly human—a genuinely civilized man. He is ever helpful—always involved in aiding those who need him at every level. His Department in London at the Royal National Orthopaedic Hospital is a temple of learning, not only for the many young British trainees in Radiology, but for myriads of visitors from the far corners of the earth. All are welcome and all gain enormously from him. He exemplifies the tradition of the true and great teacher.

No introduction of Dr. Murray would be complete without a brief reference to his intimate family. His wife, Suzette, is a distinguished physician in her own right in the field of Occupational Medicine. This charming and highly intelligent woman is a fit companion for this man—ever supportive and one whose wise counsel in all spheres has provided for him a tower of strength through the years. Their three children are fitting replicas of the parents—a fine son who is a barrister in London and two beautiful daughters, one of whom recently has

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* Presented at the Seventy-sixth Annual Meeting of the American Roentgen Ray Society, Atlanta, Georgia, September 30–October 3, 1975.

† Professor and Chairman, Department of Radiology, Montefiore Hospital and Medical Center, 111 East 210th Street, Bronx, New York 10467.

matriculated in Medicine at the Royal Free Medical School and Hospital in London. All three are married to equally fine individuals. Delightful grandchildren round out a closely knit and impressive family group.

This distinguished Society began the sponsorship of the annual Caldwell Lecture in 1920. The list of lecturers comprises a veritable galaxy of stars and is included on Pages 56–59 of your program book and need not be repeated here. Some are physical scientists whose contributions to our specialty were monumental. Most were and are radiologists—veritable "giants" in our discipline—some of whom are here today. Dr. Murray follows appropriately in their tradition. He will speak on "Iatrogenic Lesions of the Skeleton"—a logical extension of his lecture at the Radiological Society of North America meeting in Cincinnati in 1960, which dealt with the effects of steroids on the skeleton.

Ladies and Gentlemen, it is a deeply felt and never-to-be-forgotten honor and a rare personal privilege for this very close friend of long standing to be able to introduce Dr. Ronald O. Murray as the 55th Caldwell Lecturer of the American Roentgen Ray Society.

Vol. 126, No. 1

IATROGENIC LESIONS OF THE SKELETON*

CALDWELL LECTURE, 1975

By RONALD O. MURRAY, M.B.E., M.D., F.R.C.P.(Ed.), F.R.C.R., F.A.C.R.(hon.)
LONDON, ENGLAND

IN approximately nine months' time this great country will celebrate its second century of independence. During these years its contributions to the arts, to literature and, not least, to science, have been remarkable. Among the last we must emphasize the astonishing advance of our own special discipline of radiology, which, almost in geometrical progression, has become an essential component in the diagnostic and therapeutic armory of medicine today.

Eighty years have passed since the news of Roentgen's dramatic discovery was disseminated so rapidly throughout the scientific world. Among the earliest workers in this field was Eugene W. Caldwell. At the age of only 27 years and having trained as an electrical engineer at the University of Kansas, he pioneered the first radiological department in New York in 1897.

Caldwell died in 1918, at the age of 48. He was one of the early martyrs to the hazards of radiation. His dedication as a radiologist, his reputation as a teacher, and his personality as a man led in 1920 to the foundation by his colleagues of this lecture in his memory. To be invited to be that lecturer is indeed a great honor, emphasized by reviewing the list of my distinguished predecessors. Most of the Caldwell lecturers have been radiologists, but representatives of many other branches of medicine have been included. This year it is surely appropriate that we should record the recent death, in his 101st year, of Dr. W. D. Coolidge who gave us the famous x-ray tube and who presented this lecture in 1930. The list contains names familiar to us all from important contributions in the past, but within my own special interest of orthopaedic radiology I must refer to Dr. Frederick H. Baetjer, who with Dr. Charles A. Waters at the Johns Hopkins Hospital in Baltimore produced, in 1921, almost the first book on the radiology of bone disease, of which I am glad to possess an original copy. Also to be found are such names as Dr. James Ewing, Dr. Oscar Batson, Dr. Paul Hodges and Dr. Edward Neuhauser, all men who have contributed significantly to our knowledge of skeletal abnormalities.

As the fourth British subject to contribute to this series I feel especially honored. I would like to thank Dr. Ted Leigh, your President, for giving me the opportunity to address this great Society.

In these days of superspecialization, many of us tend to restrict our interests to relatively small facets of the whole discipline. As you have heard in the kind introduction by my good friend, Dr. Harold Jacobson, my own interest has been devoted to the radiological aspects of disorders of the skeleton.

Although many radiological abnormalities of the skeleton present features which are so characteristic that the diagnosis may be instinctive and immediate through recognition of a typical pattern, the interpretation of more obscure appearances usually requires correlation with certain specific items of information concerning the patient.

We must know the *sex*, since some entities have a marked affinity for either men or women. We must know the *age* of the patient, being aware that certain diseases are likely to be encountered only within fairly well-defined portions of the span of life. We will be helped by knowledge of the patient's *race* and ethnic background, since some races are peculiarly susceptible to particular disorders. Of almost equal importance is awareness of the *area of the world* in which the affected individual has lived, or has visited in these days of rapid and ubiquitous travel. Such a patient may have been exposed to a geographical hazard, often an unusual infection, such as echinococcosis. Another developing discipline in medicine, indeed, is that of geographical pathology and epidemiology. Increasing importance has been given in recent years to knowledge of the *occupation* of the patient, illustrated well by the relatively recent observation of the characteristic skeletal changes developing in workers in the chemical industry exposed to vinyl chloride monomer during the manufacture of polyvinyl chloride—a constituent of plastic materials.

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* Presented at the Seventy-sixth Annual Meeting of the American Roentgen Ray Society, Atlanta, Georgia, September 30–October 3, 1975.
From the Institute of Orthopaedics, London, England.

All these factors must be correlated with the medical history, but it is all too easy to overlook the important factor of *treatment.* To this list, therefore, I would like to add appreciation of any treatment administered to the patient prior to the radiologic examination, in order to permit due consideration of an iatrogenic cause for an abnormality. Once examined, the field is vast. This lecture considers a few of those iatrogenic lesions which involve the skeleton. This subject has continued to stimulate my interest since I had the privilege, 15 years ago, of bringing to this continent, from the other side of the Atlantic Ocean, a report on the iatrogenic disorders of the skeleton induced by steroid therapy.[40,41]

The majority of these abnormalities is attributable to trauma, either inadvertent or surgical, to iatrogenic metabolic disturbances, and to the effects of medication. When the injuries induced by irradiation are considered as a specialized form of trauma and the years that passed before its hazards were fully appreciated are recalled, a comparison can be made today with the iatrogenic effects of medication. New drugs are introduced to the medical profession with ever increasing frequency. As far as is possible their safety in use is established before their release, in your country by your ever watchful Food and Drug Administration and in mine by our National Committee on Safety of Medicines. But errors do occur, as witnessed by the thalidomide disaster in Europe and Australia just over a decade ago. We, as radiologists, must be alert to the possibilities of new iatrogenic hazards and add our efforts to the early detection of any ill effects of medication.

INADVERTENT TRAUMA—ACUTE

Injuries to the skeleton may result from therapeutic application of force. Such trauma may be acute, as in damage to the thoracic cage incurred during the emergency of cardiac massage or during psychiatric treatment, with electro-convulsive therapy being applied without the now customary use of a muscle relaxant. Under the latter circumstance posterior dislocations of the shoulder and compression fractures of the mid-thoracic vertebrae were likely to occur. Another example, by contrast, is provided by a child of eleven (Fig. 1) who presented with stiff neck, the head rotated to the right, and persistent vomiting. An atlanto-axial subluxation, present for a month, had apparently been sustained during a general anesthetic for removal of an acutely inflamed appendix. (In fairness to the anesthetists one should mention an exceptional episode of a patient who was being anesthetized for surgical excision of a prolapsed intervertebral disk. For technical reasons the operation had to be cancelled. On regaining consciousness the patient declared himself to be cured!) Unintentional acute injuries may also be sustained by forcible restraint of a struggling patient, particularly a young child (Fig. 2, *A–D*). Traumatic lesions may be inflicted inadvertently by injections. The peculiar condition of the pseudomalignant tumor of soft tissues is now well known to pathologists and is believed to follow such trauma.

The lesion bears some histological resemblance to an osteosarcoma of soft tissue[22] (Fig. 3), but differs from the entity with which it is sometimes confused—myositis ossificans or, more correctly, post-traumatic mineralization.

Rare iatrogenic complications of injection procedures include permanent anesthesia of a leg following lumbar puncture, with subsequent development of neuropathic changes in the knee joint, and accidental introduction of infective organisms, causing localized osteomyelitis sometimes simulating a bone tumor.

Repeated self-administered injections of adrenalin into the thighs of an asthmatic have culminated in massive calcification of the soft tissues, attributed to capillary spasm diminishing vascularity and, by alteration of the pH, predisposing to intramuscular deposition of calcium phosphate.[39]

INADVERTENT TRAUMA—CHRONIC

Chronic trauma, due to continued stress, also may result in bizarre roentgenologic appearances. For example, prolonged traction of a child's leg in the treatment of a tuberculous hip in the pre-antibiotic era stimulated, not infrequently, premature fusion of the distal femoral and proximal tibial epiphyses, culminating in adult life, in inequality of limb length and deformity of the knee, so increasing susceptibility to premature degenerative changes—the "traction knee."

Of more importance is the development of so-called iatrogenic Perthes' disease in the treatment of congenital dislocation of the hip. Closed reduction of such a dislocation, with immobilization of both hips in a "frog" plaster in a position of abduction and external rotation may compromise the vascular supply to the femoral heads. The ossific nucleus, therefore, may undergo avascular necrosis and develop evidence of fragmentation, failure of growth and, in due course, increased density as revascularization takes place, followed by reconstitution. Consequently, a femoral head may be permanently malformed with residual flattening. The contralateral and undislocated femoral head, being placed in plaster in a symmetrical position, usually develops a similar impairment of its vascular supply, reflected in later years by the presence of a central lucency or "ghost shadow." This lucency invariably corresponds to the size of the structure at the time when such treatment was initiated, enabling the radiologist to make a reasonably confident assessment of the age at which the condition first was recognized and treated (Fig. 4).

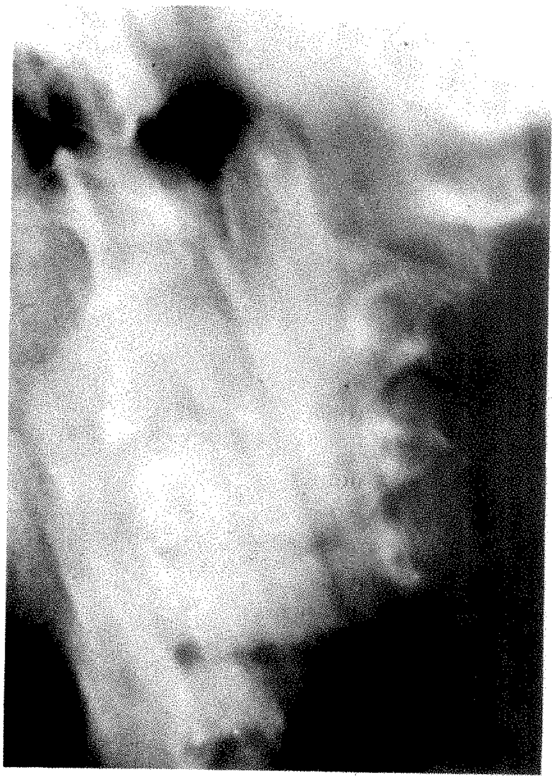

Fig. 1. *Iatrogenic trauma—acute.* This rotatory atlanto-axial subluxation appeared to have occurred during anesthesia for an appendectomy one month previously.

Gage and Winter[20] pointed out that this iatrogenic complication might be disastrous and could be avoided. In a retrospective study of 154 cases treated by closed reduction, they observed 27 completely necrotic femoral heads and 24 partially affected. By adoption of a position of immobilization

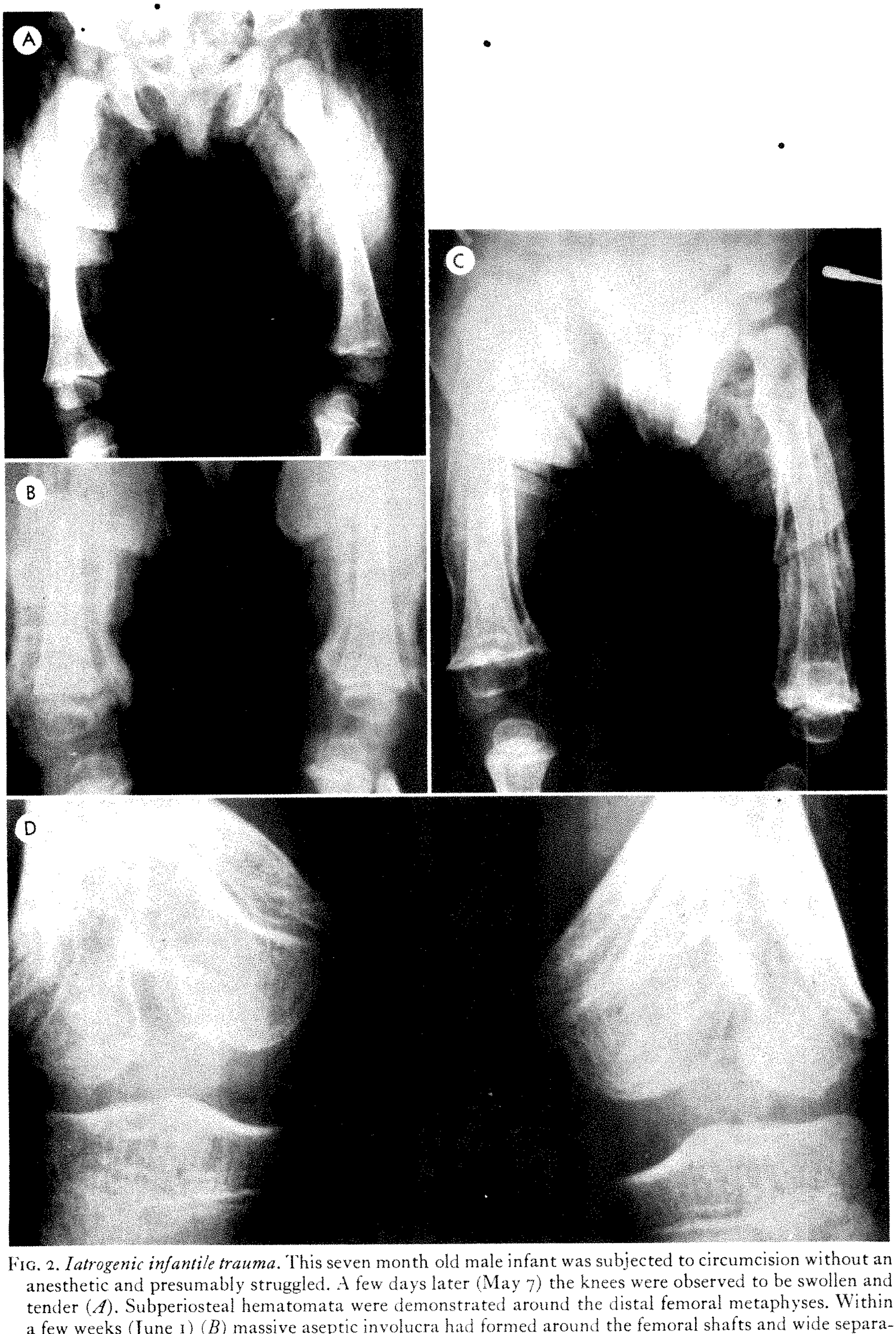

FIG. 2. *Iatrogenic infantile trauma.* This seven month old male infant was subjected to circumcision without an anesthetic and presumably struggled. A few days later (May 7) the knees were observed to be swollen and tender (*A*). Subperiosteal hematomata were demonstrated around the distal femoral metaphyses. Within a few weeks (June 1) (*B*) massive aseptic involucra had formed around the femoral shafts and wide separation of the right distal femoral metaphysis was evident. Despite satisfactory organization of these traumatic lesions (August 1) (*C*) further examination seven years later (*D*) revealed gross impairment of development of the distal femoral epiphyseal plates. Incomplete premature fusion had resulted in remarkable invagination of the epiphyseal centers into the central portion of the metaphyses. (By courtesy of Dr. John Sutcliffe,[52] Hospital for Sick Children, Great Ormond Street, London.)

with only 25° of abduction—the "human" position—the incidence of this iatrogenic complication was reduced from 48 percent in 1950 to 18 percent in 1965. Other workers have reported an incidence of this abnormality varying from only 2.5 percent[11] to 68 percent.[18] Edwards and Greidanus,[16] in reviewing 74 cases in a follow-up study 8 to 20 years after treatment, noted that 65 percent had been affected in this way. They stressed that this iatrogenic complication never occurred in untreated hips and that the ultimate prognosis was good, provided that satisfactory containment of the capital epiphysis was maintained within the acetabulum. These findings correspond to those of Kemp and Boldero,[31] who pointed out that classical Perthes' disease is associated initially with an intra-articular effusion causing impairment of the venous drainage of the femoral head. The earlier, and therefore the smaller, the epiphyseal center is at the time of the episode of avascularity, the better the outlook for its ultimate development.

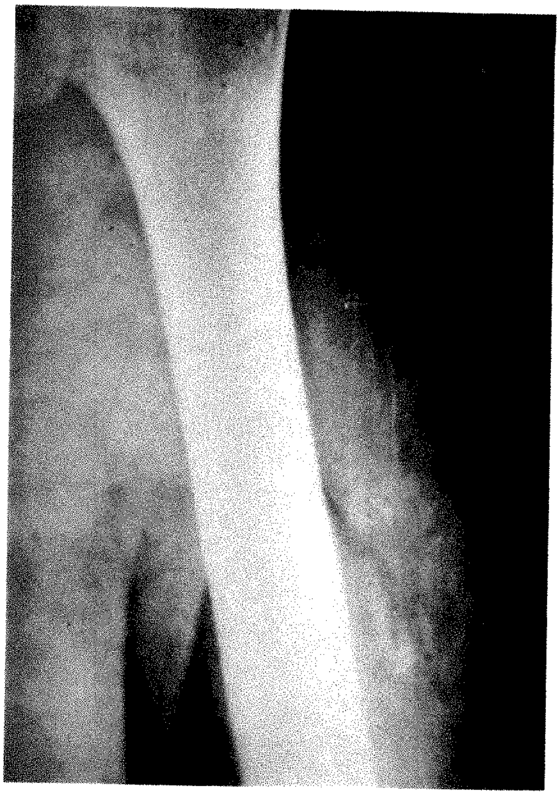

FIG. 3. *Post-injection trauma—pseudomalignant tumor of soft tissue.* A painful nodule in the arm of this young woman developed a few weeks after a prophylactic injection of gamma globulin. The dense mass was excised and histologically presented some difficulty in differentiation from an osteosarcoma of soft tissue.

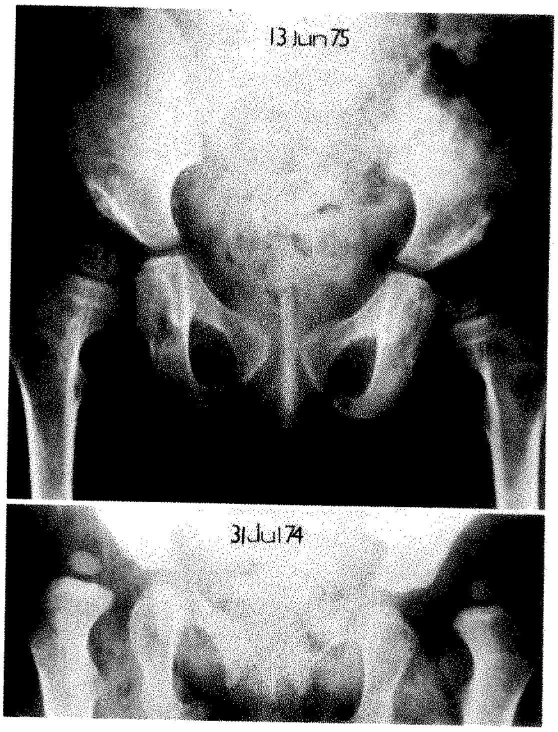

FIG. 4. *Iatrogenic trauma—chronic.* The central translucencies or "ghost shadows" in the femoral heads on June 13, 1975, correspond exactly to the size of these structures on July 31, 1974, when bilateral congenital dislocations of the hips were diagnosed. These iatrogenic abnormalities are attributable to impairment of vascular supply following immobilization in plaster in a position of full abduction of the hips.

RESIDUA OF ORTHOPEDIC PROCEDURES

The radiologist should be aware of interpreting falsely some of the bizarre appearances which may have been caused by previous operative procedures undertaken by orthopedic colleagues. The simplest example is the process of repair within a donor site for a bone graft, when a mixed pattern of sclerosis and lucency may simulate fibrous dysplasia (Fig. 5). Equally, the

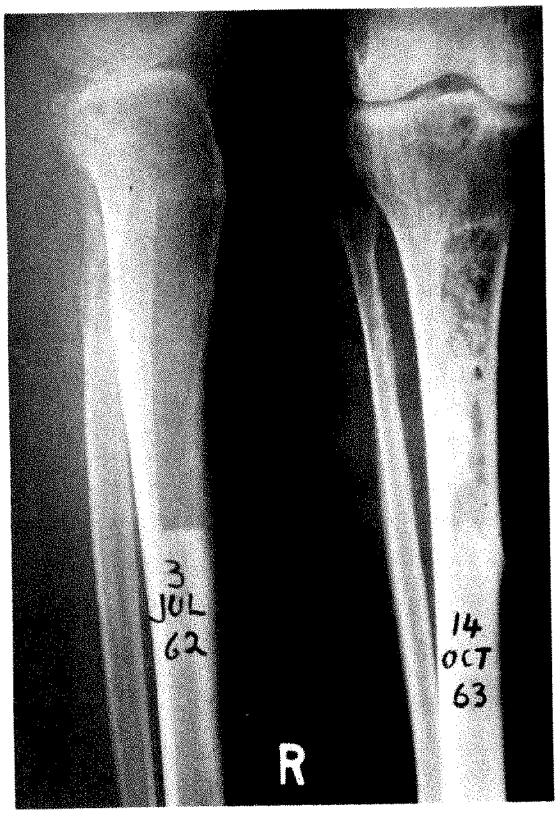

FIG. 5. *Donor graft site with stress fracture of tibia.* This lesion in the tibia was observed in a young woman complaining of chronic pain in the leg, attributed to the stress fracture at its distal end. Without knowledge of the former surgical procedure the appearance could have been confused with fibrous dysplasia.

effects of a femoral rotation osteotomy, in the course of treatment of congenital dislocation of the hip, commonly results in widening of the femoral shaft and an irregular medullary texture, again resembling fibrous dysplasia. Such lesions represent the effects of adjuvant orthopedic procedures.

Metallic implants in the skeleton are being used with increasing frequency, not only for the internal fixation of fractures and corrective osteotomies, but for the comparatively new and rapidly expanding techniques of joint replacement. The substitution of prostheses for certain neoplasms has brought with it new iatrogenic hazards. Electrolytic absorption of bone produced a destructive pattern which could be confused with an infection or a neoplasm. The use of metallic internal splints was limited on this account until 1931 when Smith-Petersen[47] introduced low chrome stainless steel, then believed to be virtually inert. Even today, however, the possibility of metal sensitivity or toxicity has been raised, opening up an entirely new field of inquiry[53]. Although in practice the incidence or failure is low, the problem must be investigated, particularly in an endeavor to explain otherwise unaccountable loosening of prostheses, with absorption of surrounding bone. Metal to metal articulations have an increased frictional resistance compared with metal to plastic joints.[2] Moreover, Coleman *et al.*[9] have demonstrated that "wear" products of metallic joint prostheses may be found in the hair, blood, and urine. Finally, a very small cloud, perhaps unimportant, must be reported on the horizon. Heath *et al.*[27] have shown that "wear" products from chrome-cobalt alloys can be carcinogenic in the rat, that animal which responds to almost any experimentally induced agent by developing tumors.

This short presentation cannot embrace routine surgical complications, such as the loosening or breaking of metallic implants and the introduction of bacterial infection. Reference, however must be made to the extraordinary appearances which may result from accidental failure to remove a surgical swab, with subsequent formation of a foreign body granuloma at the site of an orthopedic operation (Fig. 6)—a lesion described colloquially as a "cottonballoma."

EFFECTS OF RADIATION

Although some of the hazards of radiation, such as total epilation of the scalp following examination of the skull, were recognized within months of the introduction of Roentgen's new discovery, full appreciation of the hazards, not only to patients, but also to operators of the apparatus, took many years.

Almost the first man to draw attention to this danger was that great physicist, Professor Sidney Russ of the Middlesex Hospital, London, under whom, in his later years, I was privileged to study. In 1916 in the Journal of the Roentgen Society[46] he wrote on "Injurious effects produced by x-rays."

Since then the complications of post-irradiation fractures, necrosis of bone, premature fusion of epiphyses and the late development of both benign[38] and malignant tumors[6] have been appreciated. According to Philips and Sheline,[44] post-irradiation sarcoma is exceedingly rare, occurring in only two patients in almost 6,000 treated, with latent intervals of seven and eleven years. Moreover, attention has been drawn by Stewart *et al.*[50] to the danger of radiation-induced leukemia. Although it has been suggested that this iatrogenic complication has been exaggerated,[17] little

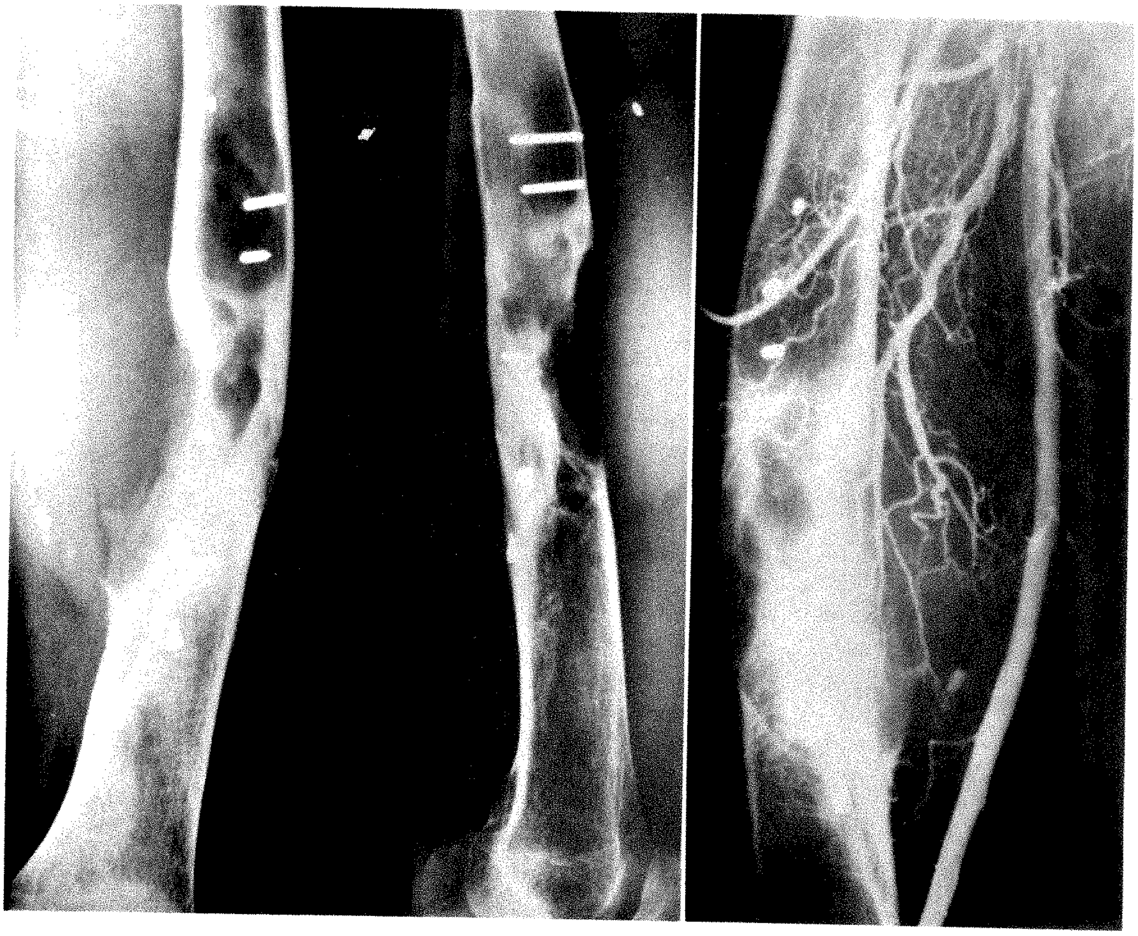

Fig. 6. *Foreign body granuloma.* In 1944, at the age of 28, this man suffered a war wound with a compound fracture of the femur. In 1949 the internal splint was removed. In 1974 he complained of a large, but painless, swelling of the thigh which had developed slowly over four years. Roentgenologically this mass was dense, with clearly defined margins, but extensive erosion of the femoral shaft was evident. An arteriogram revealed no hypervascularity in this area. Preoperatively an implantation dermoid was suggested. The mass was excised. Histologically it was encapsulated by fibrous tissue. Much necrotic tissue was present, interspersed with linear lucencies surrounded by giant cells. Examination under polarized light showed these lucencies to be due to cotton fibers, and the lesion was considered to have been caused by a surgical swab being left *in situ* at the time of the second operation—the so-called "cottonballoma." (By courtesy of Mr. A. Benjamin, Watford, England.)

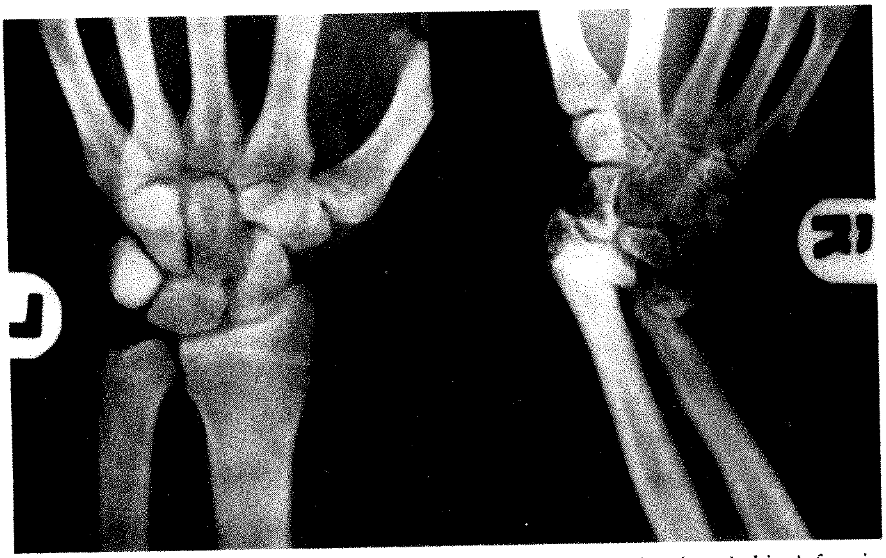

Fig. 7. *Iatrogenic effect of radiation therapy*. This 18 year old man had developed this deformity of the right wrist as a consequence of irradiation of a benign cutaneous nevus seven years before. Premature fusion of the epiphyses and arrest of osseous growth had occurred. (By courtesy of Prof. K. T. Evans, Cardiff, Wales.)

doubt exists that leukemia may be a complication of exposure to irradiation.

Irradiation diminishes mitotic activity so that viability of the irradiated tissue is reduced. The occurrence of necrosis of the femoral head following its incidental irradiation in the treatment of gynecological cancer is well known. Such therapy ultimately may result also in the presence of mixed areas of lucency and sclerosis in the innominate bones, often accompanied by pathological fractures. Without knowledge of such treatment, serious diagnostic error may result, since the lesions may be misinterpreted as metastases. The patient then may be submitted to still more, and harmful, ionizing radiation. Nevertheless, exposure to irradiation may reduce the viability and strength of bone without frank radiological evidence of necrosis. Such bone is brittle and knowledge of the history may explain the development of stress fractures of the femoral necks.[23]

Similar lesions of the bones around the shoulder may follow treatment for breast cancer. The development of increased pain and irregularity of texture of the irradiated bone, particularly with an associated soft tissue mass, must suggest a post-irradiation sarcoma. Lymphedema of the arm may also be evident, attributable in part both to surgery and irradiation. The rare complication of lymphangiosarcoma developing in the affected tissues—the Stewart-Treves syndrome—should be remembered.[14]

In children the growing epiphyseal plates are especially sensitive to irradiation, and iatrogenic disasters have occurred in the past, usually as a result of irradiation of a benign skin lesion (Fig. 7). Similarly irradiation of one side of the abdomen for a Wilm's tumor or a neuroblastoma is likely to impair growth on the adjacent side of the spine. Consequently, successful treatment has been followed by the development of a long-curve scoliosis.[43,45] Appreciation of this complication has made it uncommon.

The use of radium salts as therapeutic agents[33] for a variety of conditions between 1915 and 1931 is now historical. These salts were stored largely in the skeleton, and the alpha particles, over periods of many years, provoked an inflammatory response with fibrotic and sclerotic reactions. The therapeutic use of thorium, also long discontinued, engendered similar late changes. Both elements were likely to induce a radiation sarcoma.

IATROGENIC METABOLIC DISORDERS

Osteomalacia. The chain of events culminating in the deposition of a calcium phosphate complex in osteoid, to produce normal mineralization of bone, depends primarily on the provision of adequate quantities of calcium and phosphorus in the diet. Absorption of calcium depends on a sufficient supply of vitamin D, but absorption of this substance, being fat-soluble itself, is in turn dependent on adequate emulsification of the fat content of the diet by bile salts. Even when adequate calcium and phosphate ions have been absorbed and available, their final deposition in osteoid requires the enzyme alkaline phosphatase. Many breaks in this chain cause a large variety of metabolic disorders, largely grouped under the heading of osteomalacia, sometimes iatrogenic.

Osteomalacia Due to Therapeutic Diets. Treatment of osteomalacia by specialists in metabolic disorders is aimed at achieving normal mineralization of bone, as, for example, by the therapeutic variation of the supply of calcium and phosphorus in the diet. Such measures inadvertently may be carried to excess, with consequent development of roentgenologic abnormalities. For example, hyperphosphatemia may be treated by oral administration of aluminum hydroxide. This substance then forms insoluble aluminum phosphate in the alimentary tract so that the intake of phosphorus is diminished.[3] Such treatment is being used increasingly to prevent ectopic calcification in the soft tissues, particularly in patients undergoing renal dialysis. Conversely, persistent elevation of serum calcium may be treated by reducing the calcium content of the diet (Fig. 8). In both cases overtreatment results in a disturbed calcium-phosphate balance with consequent roentgenologic evidence of osteomalacia or rickets.

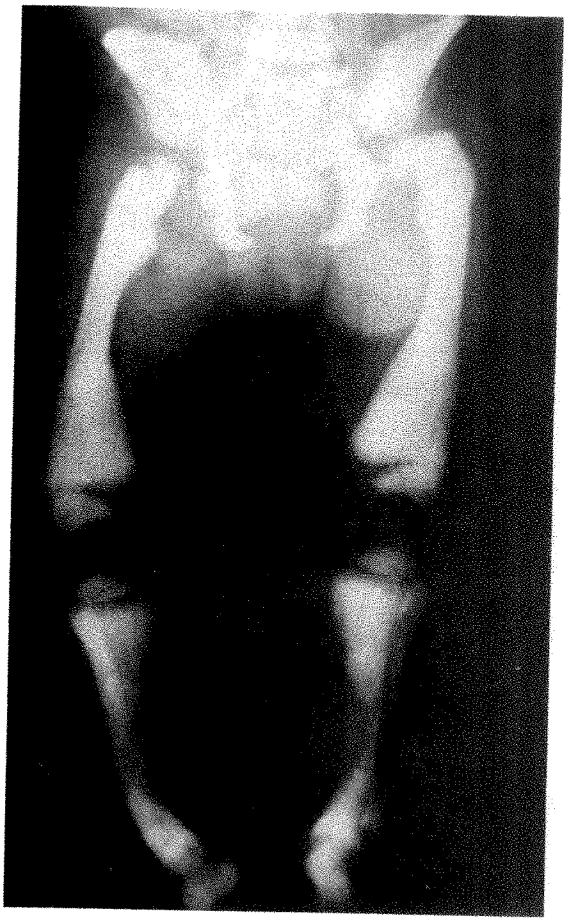

Fig. 8. *Iatrogenic rickets complicating osteopetrosis.* This six year old boy with the severe autosomal recessive form of osteopetrosis had been treated since birth with a low calcium diet. The roentgenologic features of generalized increase of bone density and flask-shaped femora are present. Superadded changes of rickets, with metaphyseal and peripheral epiphyseal lucencies were the result of this treatment which had, in fact, prolonged life beyond the expected span of three years in this condition.

Osteomalacia Due to Anti-convulsant Drugs. The metabolism of vitamin D is now recognized to be extremely complicated, but the necessity for this vitamin for normal metabolism obtained either in the diet or by synthesis in the skin by the action of sunlight on the provitamin, 7-dehydrocholesterol, has been appreciated ever since the classic report of Mellanby in 1919.[35] Among the new facts concerning this vitamin is the relatively recent recognition that its normal conversion in the liver to 25-hydroxycalciferol is affected by

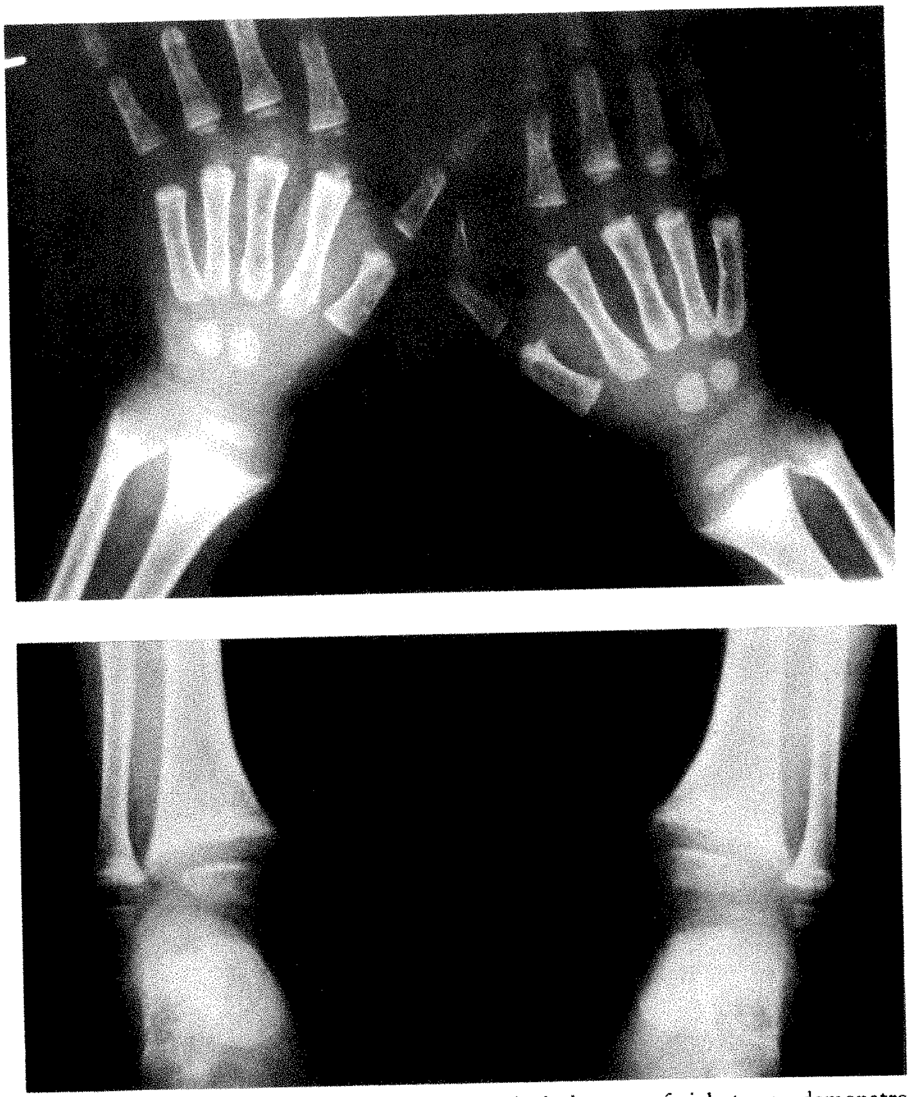

FIG. 9. *Iatrogenic rickets due to anti-convulsant drugs.* Typical changes of rickets are demonstrated in this epileptic child who had been treated with phenytoin since birth. (By courtesy of Dr. Guy Harper, Wellington, New Zealand.)

anti-convulsant drugs (particularly phenytoin) so that a relative vitamin D deficiency is induced with consequent clinical and roentgenologic manifestations of osteomalacia and rickets (Fig. 9). This iatrogenic hazard was reported first by Kruse in 1968,[32] when he observed roentgenologic and biochemical changes of rickets in 15 percent of young epileptics, the degree of severity being dependent on the dose and duration of administration of anti-convulsant drugs. This problem was studied by Dent and his colleagues[13] who suggested that increased inactivation of vitamin D in these patients was due to a drug-mediated enzyme induction. Iatrogenic osteomalacia has been observed also to develop during prolonged therapy with other drugs. A synergistic action between barbiturates and phenytoin has been suggested.

Postgastrectomy Osteomalacia. General surgical procedures may induce their own metabolic disturbances. Osteomalacia developing in patients who had been subjected some years previously to gastrectomy, or extensive intestinal resection, has been reported from many parts of the world with some controversy concerning its incidence.[7,36,37] Eddy,[15] however, reported in 1971 that 30 percent of a series of 342 postgastrectomy patients had defects of calcium metabolism as opposed to five percent of 123 control patients with peptic ulcers treated without surgery. He claimed that osteomalacia might develop in 25 percent of postgastrectomy patients. The follow-up period ranged from two to 20 years with a mean of 7.4 years. Roentgenologic evidence of demineralization was evident in 25 percent, pathological fractures in 5.8 percent, but Looser's zones in only 2.4 percent.

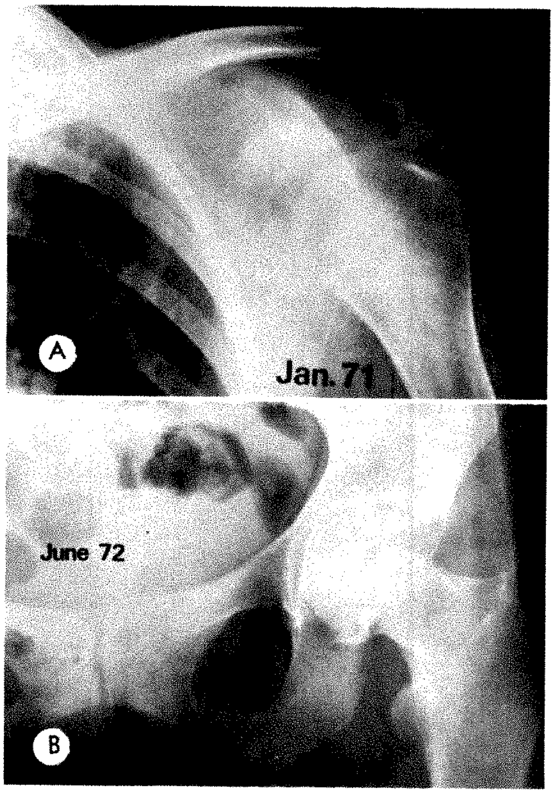

Fig. 10. *Postgastrectomy osteomalacia with secondary hyperparathyroidism.* (*A*) This expanding osteolytic lesion in the scapula of a 54 year old woman had enlarged considerably during the previous two years. The biopsy was interpreted erroneously as a malignant bone tumor and scapulectomy was performed. (*B*) Eighteen months later increasing weakness, diarrhea and bone pain prompted a skeletal survey which revealed a Looser zone in the left femoral neck. Biopsy then confirmed the presence of osteomalacia, attributed to a partial gastrectomy 26 years previously. The scapular lesion was a brown tumor of hyperparathyroidism.

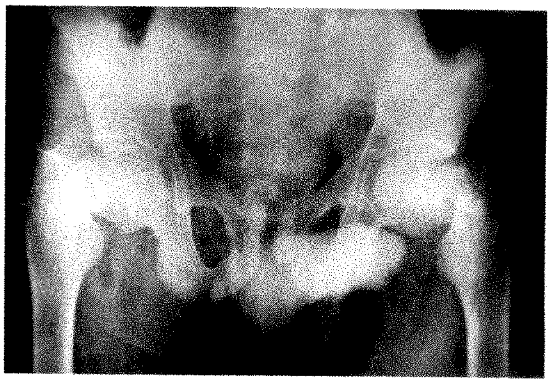

Fig. 11. *Fractures of femoral necks due to tetany following inadvertent total parathyroidectomy.* This 28 year old man on renal dialysis developed secondary hyperparathyroidism. Parathyroidectomy was inadvertently total so that a marked fall in serum calcium induced tetanic spasms, sufficiently severe to fracture both femoral necks. (By courtesy of Dr. Phillip Jacobs, Birmingham.)

Postgastrectomy osteomalacia may be complicated further by secondary hyperparathyroidism, even with brown tumor formation (Fig. 10, *A* and *B*).

Another interesting iatrogenic hormonal disturbance is that caused by inadvertent total parathyroidectomy in the treatment of hyperparathyroidism. Lack of parathyroid tissue causes the circulating parathormone level to fall fairly rapidly, with blood calcium levels being reduced to four or even less. The inevitable consequence is tetany, accompanied by generalized muscle spasm, sometimes sufficiently severe to cause pathological fractures (Fig. 11).

Iatrogenic Osteoporosis. The most important cause of iatrogenic osteoporosis is steroid therapy. The isolation of cortisone, first known as Compound "E," by Hench and his colleagues[28] was a milestone in medicine. Its first clinical use, on September 21, 1948, in the treatment of a young woman suffering from severe rheumatoid arthritis, was miraculously beneficial. During the following decade isolated reports of iatrogenic complications began to accumulate in the world literature. The hazards of

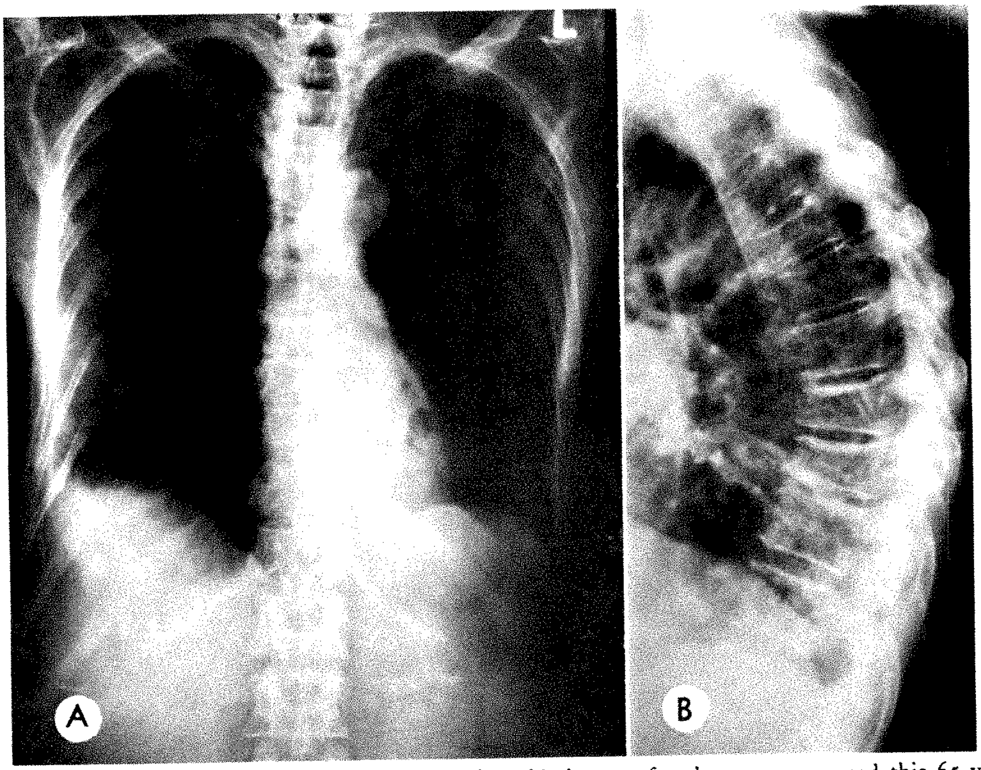

FIG. 12. *Iatrogenic Cushing's syndrome.* (*A* and *B*) Steroid therapy for three years caused this 65 year old woman with rheumatoid arthritis to develop frank obesity and hypertension. In addition to gross osteoporosis, many of the vertebral bodies suffered compression injuries with the incompletely formed callus causing the typical sign of "marginal vertebral condensation." Many fractures of the ribs were present and a lung abscess was evident in the left lower lobe. These lesions were all virtually asymptomatic, owing to suppression of the sense of pain by the steroid therapy.

prolonged steroid therapy are now widely appreciated.[40,41] With reduction of osteoid formation, generalized osteoporosis develops, entirely comparable to Cushing's syndrome of natural origin. Pathologic fractures are common and show delayed healing with pseudocallus formation (Fig. 12, *A* and *B*). The secondary effect of these hormones is to suppress the sense of pain. Many of the fractures, particularly of ribs, are consequently asymptomatic and may be recognized only incidentally. When these fractures involve articular surfaces, gross disintegration of joints may take place, sometimes without painful symptoms. Such pain as is present usually appears to be much less severe than the roentgenologic pattern might suggest. The appearance, therefore, with one striking exception, simulates that of the true neuropathies of neurosyphilis and syringomyelia. The exception is provided by the lack of reactive sclerosis often seen in this condition, coupled with the presence of generalized osteoporosis. The weight-bearing joints of the leg are most commonly affected, especially the hip. In many cases the joints previously have been normal, but such involvement is more frequently encountered in a joint ravaged by rheumatoid arthritis.[54] Articular disintegration of this type may be observed even in the wrists, when a patient crippled by the disease has been ambulant only with the aid of canes, thus exposing these joints to the stress of weight-bearing.

These destructive changes are especially common after renal transplant surgery, when high doses of steroids are employed to combat rejection phenomena (Fig. 13).

The incidence of this complication has varied in different centers,[12,48] ranging from four to 20 percent, with an apparent increase as the success rate of the transplant procedure rises.

In children, particularly those with Still's disease, steroid therapy impairs growth. The paradoxical situation may then arise in which epiphyseal centers mature early because of hyperemia around affected joints, but are smaller than normal because their development is delayed by steroid therapy (Fig. 14).

In addition to diminishing pain sense, steroid hormones also have an anti-inflammatory effect so that infective lesions may spread silently and at an alarming rate. Reactive new bone formation, frequently demonstrated roentgenologically with pyogenic infections, is virtually absent, so that these infective foci may resemble tuberculous lesions.

As an iatrogenic complication, osteoporosis has been observed also as a result of prolonged heparin therapy in the treatment of thrombo-embolic disease.

Stinchfield and his colleagues[51] were the first to draw attention to delayed healing of fractures in patients receiving anticoagulant treatment and supported their suspicions by convincing animal experiments. A decade later a detailed investigation by Griffith *et al.*[26] showed that the development of such osteoporosis was related to dosage. Patients receiving 10,000 units, even for periods of many years, were unaffected, but the majority of those treated with doses ranging from 15,000 to 30,000

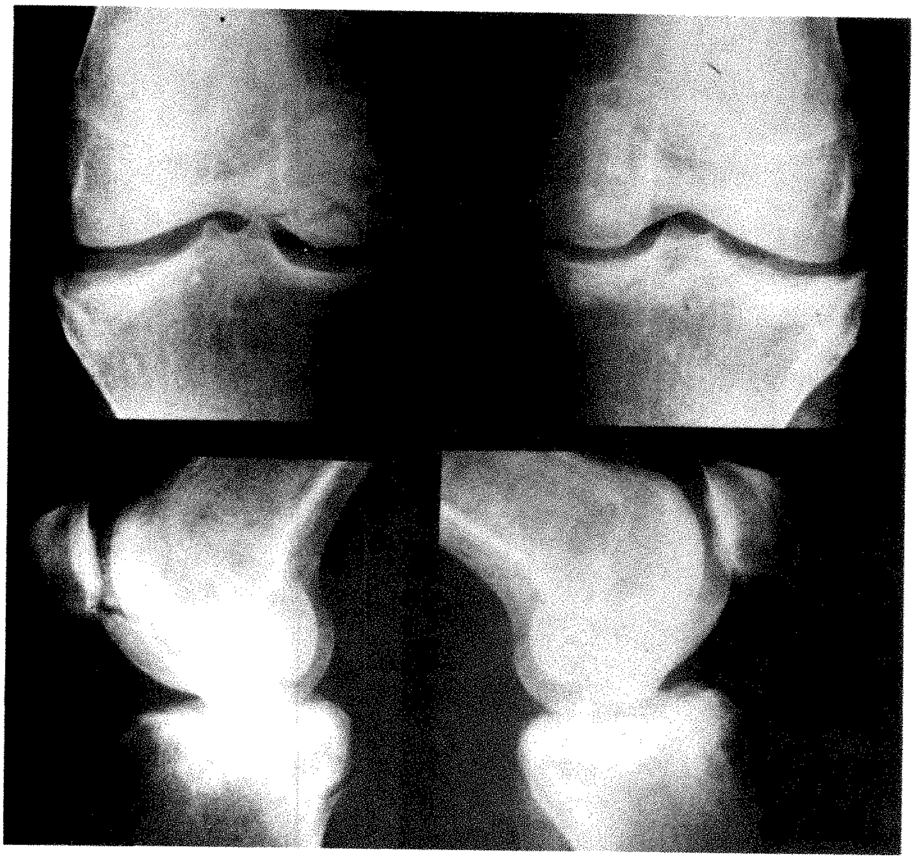

Fig. 13. ***Steroid arthropathies following renal transplantation.*** The hips and knees of patients maintained on large doses of steroids following organ transplantation frequently disintegrate. Eighteen months after the surgical procedure, marked fragmentation of the articular surfaces of both knees was demonstrated in this patient. Painful symptoms were present.

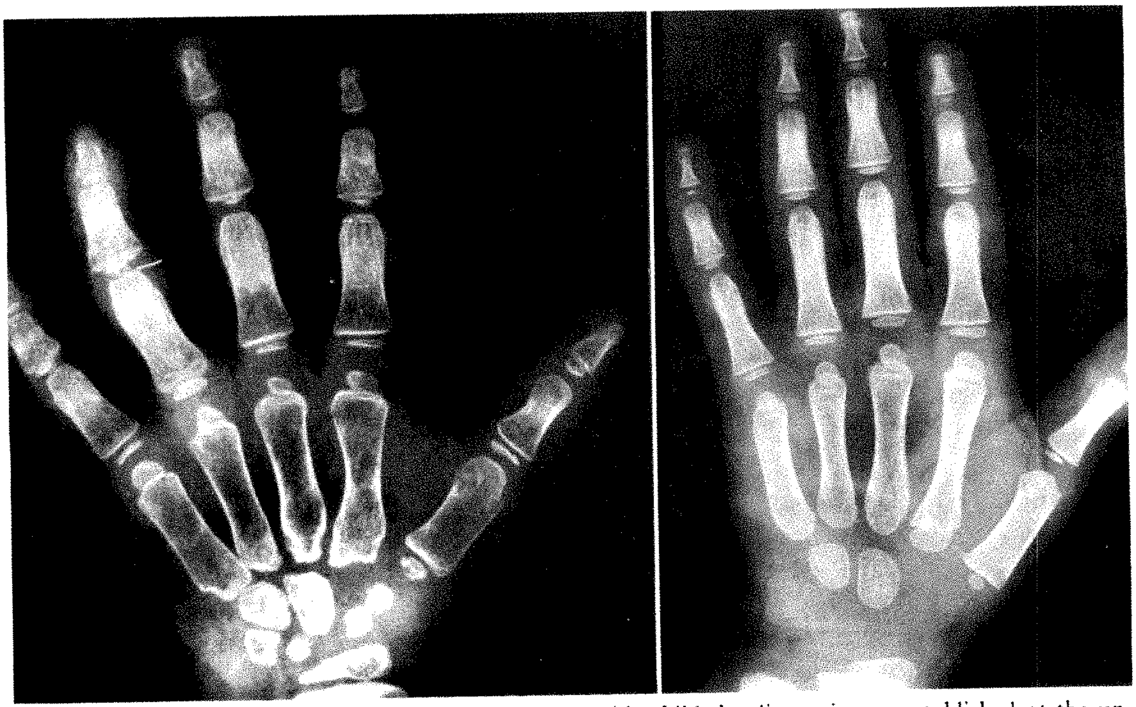

FIG. 14. *Still's disease with iatrogenic hypercorticism.* In this child the diagnosis was established at the unusually early age of nine months. At the age of two years ossification was consistent with a skeletal age of six years, but the carpal bones of the involved and swollen joint were all diminutive in size. This paradox appeared to be explained by the hyperemia of the inflammatory process which induced premature ossification, but growth was delayed by the steroid therapy. Contrast the appearance with the control roentgenogram a normal child of the same age and sex.

units daily developed severe osteoporosis, frequently accompanied by spontaneous fractures of vertebral bodies and ribs. Goldhaber[21] suggested that heparin might be a co-factor with parathormone in stimulating severe resorption of bone.

EFFECTS OF MEDICATION

Vitamin D Intoxication. In the treatment of metabolic bone disease, vitamin D is a favorite therapeutic weapon. Extreme overdosage of the order of 4–18 million units daily has caused renal damage with clinical features of headache, drowsiness, and gastrointestinal disturbance and with gross alterations in blood chemistry, resulting in extensive calcified deposits in soft tissues.[8]

Vitamin A Intoxication. The historical iatrogenic error of vitamin A poisoning, described by Caffey in 1951[4] may be recalled. Prolonged overdosage of this vitamin was usually due to confusion of a vitamin concentrate, oleum percomorphum, with cod liver oil. Young children, to whom, in the cause of good health, this treatment was administered over periods of months, developed extreme irritability. Tender bone swellings, particularly in subcutaneous areas, were demonstrated roentgenologically. Griffin[25] noted another complication of this disorder, observing invagination of the distal femoral metaphyses and premature epiphyseal fusion. Freiberger, however, reported excellent remodelling and almost normal development in follow-up studies of one of these children in adult life.

Heavy Metal Poisoning. In the pre-antibiotic era the therapeutic use of bismuth for congenital syphilis was liable to cause metaphyseal densities in children comparable to those observed in lead poisoning.[5] Another historical example of poisoning of this type was that caused by excessive administration of phosphorized cod liver oil.[43]

Iatrogenic Arthropathies. In the introduction to this lecture, reference was made to a host of new drugs which are constantly being made available. In preparing a thesis for the degree of doctor of medicine, in the late 1950's, on the effects of steroids on the skeleton, roentgenograms of many patients with degenerative joint disease of the hip were examined. The objective was to find those patients in whom the worst destructive changes developed without exhibition of steroids. Two of these cases were selected for publication. During the subsequent decade, the incidence of patients with "crumbling hips," to whom steroids had never been administered, appeared to increase continually. This phenomenon had not been observed with any degree of frequency by my senior colleague, Dr. E. H. Allen, or myself during our earlier professional years. It was believed, therefore, that this apparently new entity represented another form of "analgesic arthropathy" and the appearance became sufficiently characteristic for this diagnostic term to be employed. In reviewing the two cases just mentioned, it was discovered that both these patients had been among the earlier recipients of phenylbutazone therapy. The analgesics believed to be mainly responsible are phenylbutazone (Fig. 15) and indomethacin, but both these drugs frequently have been administered to the same patient, often in combination with other analgesics. A few cases were considered to be attributable to chronic alcoholism in which condition suppression of pain sense may be a part of a peripheral neuropathy. In this instance the hypothesis that subarticular infarction may be due occasionally to fat embolism may well be correct, in view of the frequency of an associated chronic pancreatitis, although subclinical unrecorded trauma probably plays the principal role in such instances of infarction in alcoholics. Chronic alcoholism is no new disease and it was suspected that such cases in the past had been filed in our radiologic museum under the diagnosis of "atypical Charcot joints." One hundred of these patients were investigated and the results reported (Table 1) to the Meeting of the European Association of Radiology in Amsterdam in 1971.[1]

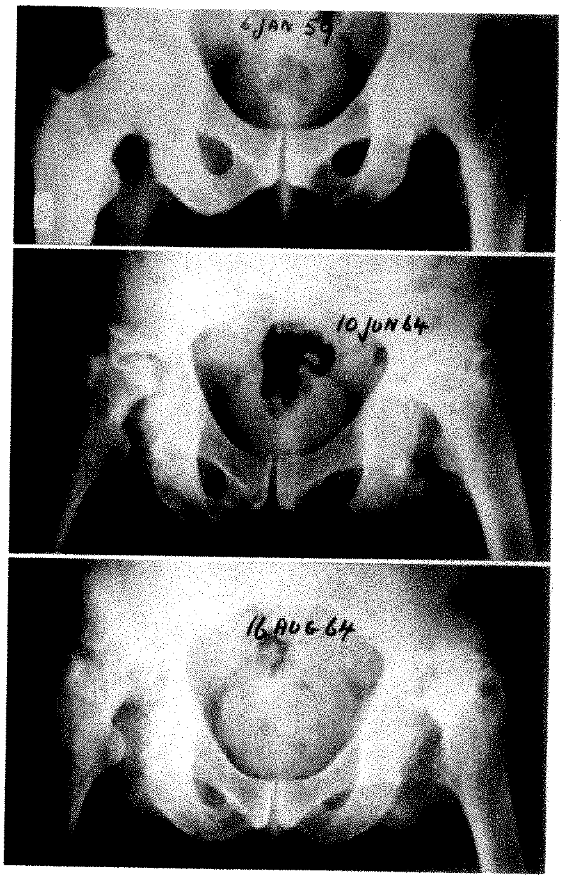

FIG. 15. *Analgesic arthropathy of the hips associated with phenylbutazone therapy.* At the age of 65 this man developed painful degenerative changes in both hips. Almost complete symptomatic relief was obtained by medication with analgesics during the subsequent five years. During this time he had consumed no less than 700 grams of phenylbutazone. Bilateral total hip replacements were then performed with clinical success. (By courtesy of Mr. D. E. Macrae, Southampton.)

Effects of Medication During Pregnancy. Many reports have emphasized that treatment of the pregnant woman also affects the fetus. The use of drugs during pregnancy continues to increase, almost to the point of medical pollution. The size of the problem was emphasized by Forfar and

TABLE I

100 ARTHROPATHIES*

Medication	No. of Patients
Steroids	26
Phenylbutazone	32
Indomethacin	25
Analgesics unspecified	8
Other analgesics	5
No analgesics	4

* Allen, E. H. and Murray, R. O. Iatrogenic arthropathies. Proceedings of the European Association of Radiology, Amsterdam, 1971. Excerpta Medica, Amsterdam.[1]

Nelson[19] who, investigating 911 randomly selected pregnant women, found that 82 percent of these patients gave a history of taking some drugs, with an average of four. Those used most commonly, iron and vitamin preparations, were followed by analgesics. Stern[49] stated "Western Society, which is relatively materialistic in the eyes of the world, has become accustomed to the idea that there must be a cure for everything and that every complaint, no matter how small, deserves a pill, a potion of some other kind of medication."

This attitude appears to constitute a major medical problem affecting all our disciplines. Some warning has been given about a latent interval in the work of Herbst *et al.*[29] who noted an association between mothers given diethylstilbestrol during pregnancy and the development in their daughters, 20 years later, of vaginal adenocarcinoma.

Teratogenic Drugs. The thalidomide disaster will not easily be forgotten. This effective sedative was used to induce sleep. The first trimester, particularly during the fourth to seventh weeks, is the period in which the limb buds form. If the drug was consumed at this time, reduction deformities of the limbs resulted (Fig. 16). Many cases occurred in Europe and Australia. The United States was fortunately exempt as the F.D.A. had prevented its use because of a correct suspicion that this sedative induced a peripheral neuropathy. McCredie, and McBride[34] have suggested that chemical injury to the neural crest inhibits migration of its cells for the sensory nerve of the appropriate segment, so that its trophic action is diminished and the tissues normally supplied by that nerve are deficient in growth. In their study, they noted marked frequency of radial aplasia, suggesting involvement of the 6th dermatome. Their hypothesis opens up a very wide field for investigation of reduction abnormalities which, in the past, have been dismissed casually as being congenital.

Some doubt has also been raised about possible teratogenic effects of phenytoin (already mentioned as a cause of osteomalacia in the treatment of epilepsy) and other similar drugs. Several cases of brachydactyly, with defective ossification of the distal phalanges have been observed in the children of mothers using this drug in pregnancy (Fig. 17). Recent reports have implicated warfarin, administered to the pregnant mother, in the development of Conradi-Huenermann chondrodysplasia, or an abnormality of similar appearance, in the neonate.[55]

Where are we now? Reports of suspected teratogenic disorders abound. The Committee on Safety of Medicine, for example, has recently issued a warning concerning a possible increased incidence of congenital abnormalities associated with the use of mixtures of an estrogen and a progestogen

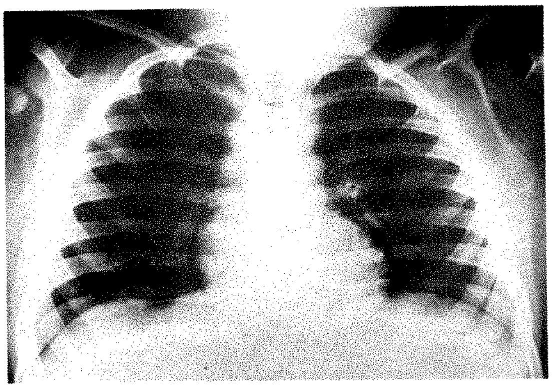

FIG. 16. *Thalidomide embryopathy*. Extreme phocomelia of both arms (and legs) were evident in this patient. These typical reduction deformities were caused by maternal consumption of this teratogenic drug, particularly during the fourth to seventh weeks of pregnancy, the period at which the limb buds form.

as a means of diagnosing pregnancy.[10,24]

We radiologists, I repeat, must be on the alert to recognize unusual, or even possibly familiar, abnormalities. Are some of these, for which at present we recognize no cause, in fact iatrogenic? During recent years, for example, unexplained bilateral and symmetrical necrosis of the femoral heads has been observed to develop during pregnancy.[30] Is this iatrogenic?

The radiologist, by a suitable display of intellectual suspicion, may be able to instigate appropriate clinical and epidemiological investigations. The incidence of these drug-induced iatrogenic lesions then may be reduced, or even eliminated, as hazards to generations of the future.

The author wishes to acknowledge with gratitude the generosity of many colleagues who have contributed material to the Radiological Museum of the Institute of Orthopaedics, London, from which the illustrations have been obtained. . . . He would like also to thank Miss J. A. MacDonald and Miss Veronika Aurens, for secretarial assistance, and Mrs. Uta Boundy, of the Department of Medical Photography, for preparation of the illustrations.

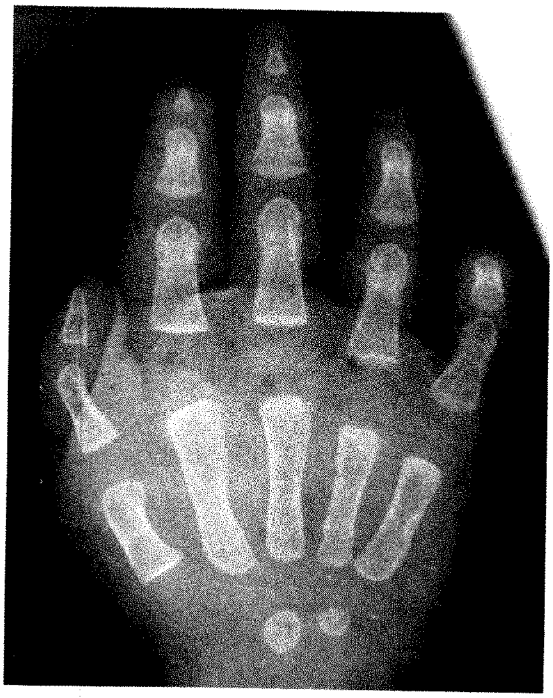

Fig. 17. *Brachydactyly due to maternal consumption of phenytoin during pregnancy.* The terminal phalanges are grossly hypoplastic. The nails had failed to form. (By courtesy of Dr. Andrew Poznanski, Ann Arbor, Michigan.)

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IDIOPATHIC MULTICENTRIC OSTEOLYSIS*

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ABSTRACT:

A 59 year old white female with striking carpal and tarsal osteolysis is reported. The process primarily involves the carpals and tarsals but includes other sites. The pertinent literature is reviewed and a simplified classification of idiopathic multicentric osteolysis is presented. Idiopathic multicentric osteolysis may be sporadic but can demonstrate either dominant or recessive inheritance. There may or may not be associated nephropathy. The underlying mechanism appears similar in all variations of this condition. Gorham's disease, the Winchester syndrome, and other osteolytic conditions which may predominantly affect the tarsal and carpal bones most likely are totally different processes, unrelated to idiopathic multicentric osteolysis.

IDIOPATHIC multicentric osteolysis (IMO) is a rare disorder leading to extensive bone loss, most frequently in the carpal and tarsal areas. It is distinguished from Gorham's massive osteolysis in that the latter is unicentric and pathologically is associated with hemangiomatosis. Several classifications of IMO have been offered. The basic pathogenetic mechanism is unknown. The disease entity is of clinical significance because it can be associated with fatal renal disease.

The purpose of this paper is to report a striking case of IMO, to review the pertinent literature, to propose a simplified classification of IMO, and to proffer a theory of pathogenesis.

REPORT OF A CASE

Case I. A.C. is a white female, currently 59 years old, who presented at the age of 56 with bilateral staghorn renal calculi. Her physical appearance is striking. She is approximately four and one-half feet tall and has a peculiar facies with frontal prominence (Fig. 1). There are marked deformities and foreshortening of her forearms (Fig. 2) and feet. Multiple transverse creases are present in the overlying soft tissues. The feet are held in a varus position. Despite her appearance, the patient has only minimal functional loss. She is even able to sew. The forearms extend and retract in an accordion-like manner when she picks up an object.

Nonunion of the midshaft of the right femur resulted from a fracture incurred from a fall in 1957 which has left the patient nonambulatory; however, before this injury she had no difficulty using her lower extremities. In fact, it is said that in her youth she not only entered foot races but frequently won them.

Other family members were similarly affected. The patient's father was similar in appearance and is said also to have had no functional impairment. The patient reports two affected siblings but, unfortunately, they have not been in contact with the patient since childhood. The patient has one son who is of normal appearance.

Roentgenograms of the left upper extremity reveal a striking loss of bone with telescoping of the soft tissues (Fig. 3). The carpals are absent. Residual portions of the metacarpals are thin and taper proximally. The phalanges are demineralized and somewhat narrowed but, in comparison with the proximal portion of the hand, are relatively intact. Most of the radius and ulna is absent. A radial head articulates with the distal humerus and a distorted fragment of bone which probably represents the ulna remains. The distal humerus, by compari-

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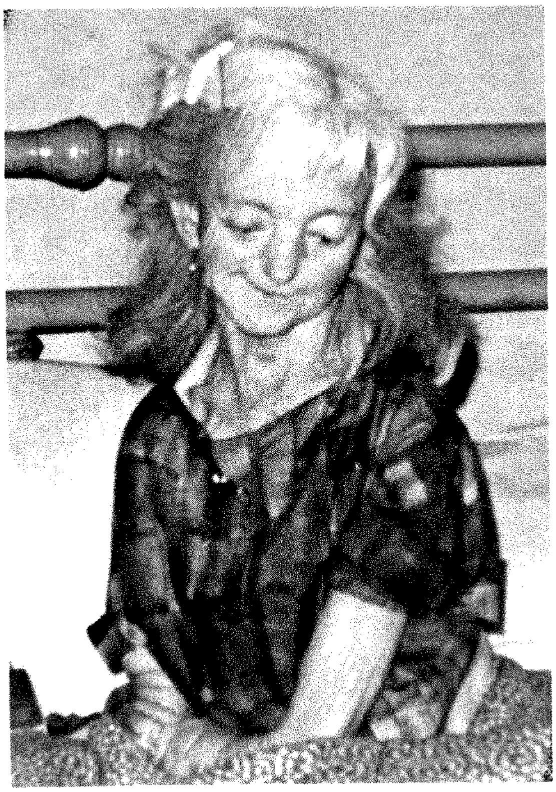

FIG. 1. Photograph of patient illustrating the peculiar facial appearance with frontal prominence. Note telescoping of forearm soft tissues.

son, is normal except for demineralization.

The right upper extremity is less markedly affected (Fig. 3). There are no carpals present, and residual portions of the metacarpals are markedly distorted. Again, there is thinning of the phalanges with demineralization. The distal radius is strikingly distorted and thin. The distal ulna is tapered. There is ulnar deviation of the hand. No formed bony elbow joint is visible, and only a small fragment of bone is seen in the elbow area. The distal humerus is resorbed and rapidly tapered. There is telescoping of soft tissues.

A roentgenogram of the right foot and ankle (Fig. 4) reveals a distorted ankle joint. The posterior portion of the calcaneus is intact but its anterior portion is absent. Distortion of the distal tarsals prevents definite identification of the individual bones. Nevertheless, the remaining bony ossicles, some of which are metatarsals and some phalanges, are thinned and distorted. Foreshortening of the foot with telescoping of the soft tissues is evident. The left foot (Fig. 5) has a similar appearance. There is no visible ankle joint and more extensive changes of the mid and anterior calcaneus are noted.

A roentgenogram of the chest (Fig. 6) reveals resorption of the right humeral head and a distorted right shoulder joint. The left humeral head is much less affected. The clavicles and ribs show demineralization and thinning.

CLASSIFICATION

Several different terms have been used for this entity including idiopathic osteolysis;[22,30] essential osteolysis;[16,17,24,33] progressive essential osteolysis;[20] essential acroosteolysis;[18] hereditary osteolysis;[13,29] familial osteolysis;[9] hereditary multicentric osteolysis;[32] carpal and tarsal agenesis;[22] bone agenesis;[26] familial dysostosis carpi;[4] and bilateral carpal necroses.[3] We propose the all-inclusive term of idiopathic multicentric osteolysis (IMO) for this entity.

IMO can then be further classified into two basic types (Tables I; and II): multicentric osteolysis with nephropathy (MON);

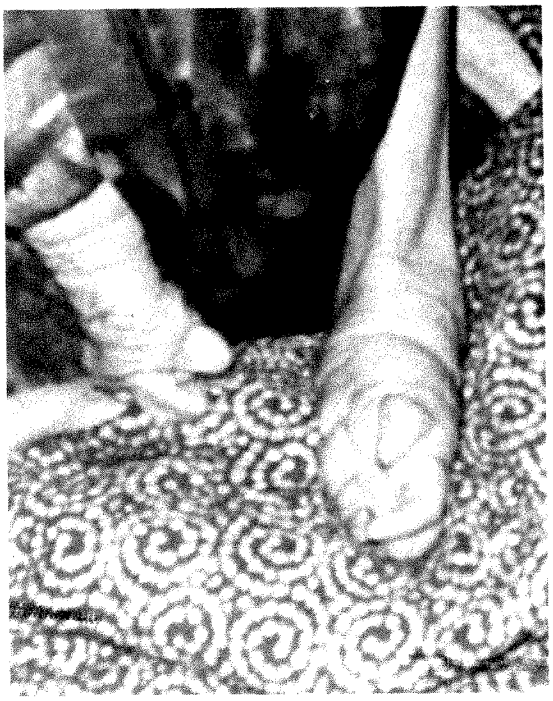

FIG. 2. Close-up photograph of the patient's upper extremities emphasizes forearm shortening. The hands are functional. Upper extremity activity causes the telescoped skin to move in an accordion-like manner.

and hereditary multicentric osteolysis (HMO). These two types can be clearly differentiated on clinical grounds. Those with nephropathy have proteinuria and renal failure which in three of the five reported cases[14,16–20,24] has been fatal by the third decade. They have no significant family history of either osteolysis or renal disease. The second group (HMO) is clearly defined by its occurrence in families, with most cases having shown dominant transmission although the trait was recessive in one family.[32] The massive osteolysis described by Gorham *et al.*[11] is not included in this classification because of its unicentric nature. The Winchester syndrome[34] also is excluded because of its differing clinical presentation and the fact that the carpotarsal osteolysis is accompanied by profound generalized osteoporosis and significant destruction of other joints which simulates rheumatoid arthritis.

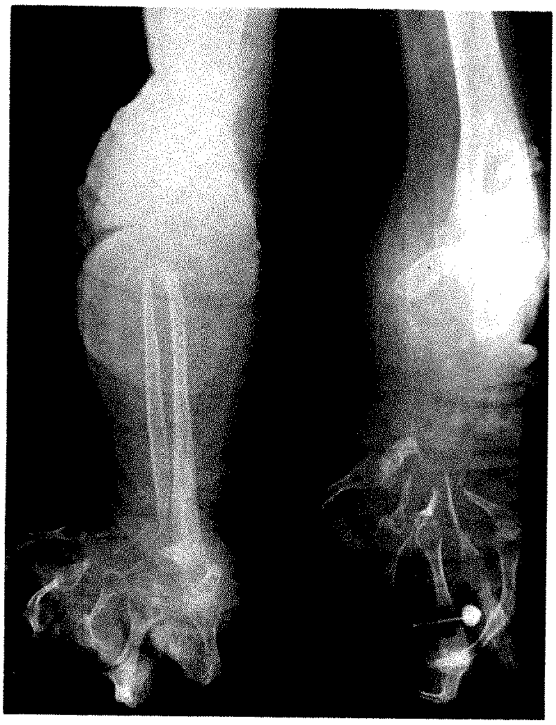

Fig. 3. The left carpus (reader's right) has virtually disappeared. Only remnants of the proximal radius and ulna remain. The left metacarpals are tapered proximally. The phalanges are relatively well preserved. The less severely affected right forearm shows absence of the distal ulna, ulnar deviation of the hand and extensive loss of the carpals and metacarpals. No bony elbow joint remains. The right humerus is shortened distally and tapers.

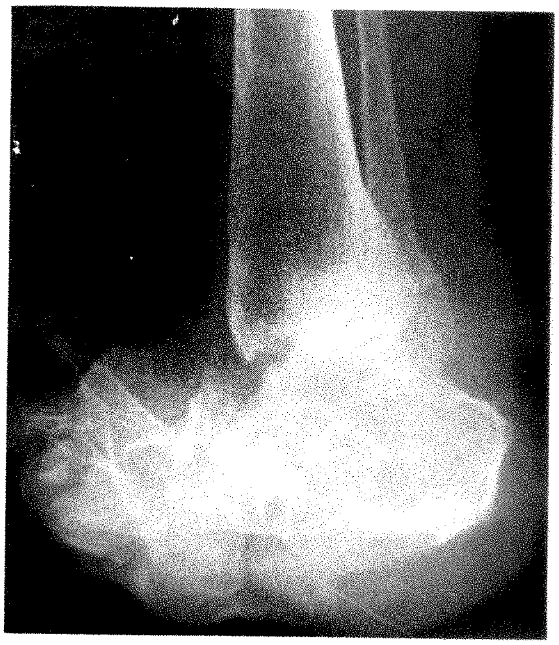

Fig. 4. Lateral view of right foot and ankle demonstrates relative preservation of posterior tarsus in contrast to marked distortion of anterior tarsus and metatarsals. The soft tissues are telescoped.

The attractive feature of this classification of multicentric osteolysis is its simplicity. Spranger and associates'[30] classification is eponymic in approach and includes entities other than multicentric osteolysis. The nomenclature of constitutional disorders of bone as modified by McKusick and Scott[22] separates idiopathic osteolysis into two types: acro-osteolysis and multicentric osteolysis. The acro-osteolysis is further subdivided into a phalangeal type and a carpo-tarsal form with or without nephropathy. We consider the terms carpo-tarsal osteolysis and idiopathic multicentric osteolysis synonymous, and IMO is preferred because the osteolysis is not isolated to the carpal and tarsal areas.

Edeiken and Hodes[6] described two types of essential osteolysis: a hereditary type transmitted by an autosomal dominant mode; and a nonfamilial type associated

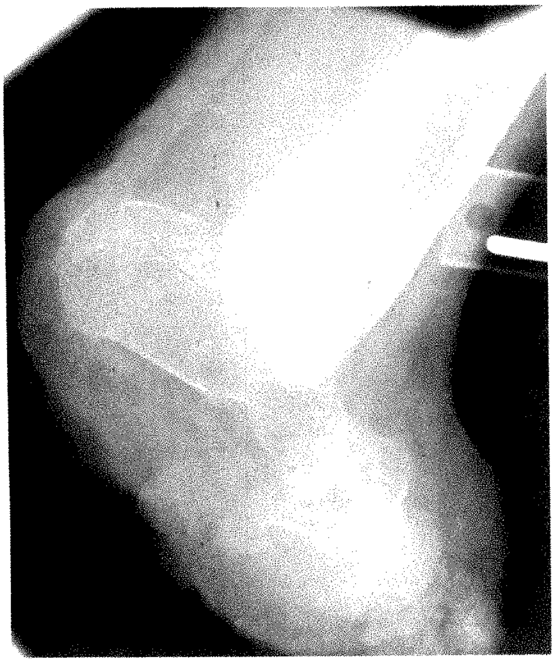

FIG. 5. Lateral view of left foot and ankle shows loss of ankle joint space and more severe involvement.

with fatal nephropathy. Our classification is similar except that we use different terminology, and the hereditary type has been shown to be either dominant or recessive.[32] Torg *et al.*[32] classify osteolysis into four types: Gorham's massive osteolysis; essential multifocal osteolysis with nephropathy; idiopathic hereditary osteolysis with dominant transmission; and idiopathic multicentric osteolysis with recessive transmission. Macpherson *et al.*[16] expanded Torg's classification to include the Winchester syndrome as a fifth type.

MULTICENTRIC OSTEOLYSIS WITH NEPHROPATHY

There have been five cases of this entity described.[5,14,16–20,24,33] The cases are summarized in Table 1. Multicentric osteolysis with nephropathy is characterized by an early onset (at the age of two years in two of the five reported cases) with swollen, deformed, painful wrists. There is progressive disappearance of the carpals and tarsals with the carpals more markedly affected. The adjacent tubular bones are involved and present a "sucked candy" tapering of the proximal metacarpals, proximal and distal shortening of the ulnae, radii of normal length, and ulnar deviation of the hands. The patients usually exhibit abnormal renal function at about the time of the onset of the bone resorption. The ensuing nephropathy has been fatal in at least three of the five cases. No hereditary tendency has been noted. Congenital foot deformities are frequently associated[16] and Torg and Steel's[33] cases were described as having a characteristic Marfan-like appearance. Renal findings at autopsy have revealed chronic glomerulonephritis. No pathologic evidence of hemangiomatosis has been reported.[14] The involvement of the adjacent tubular bones has been said to be characteristic[32] and to differentiate MON from HMO. However, Kohler and associates[13] have shown short ulnae with ulnar deviation in cases of multicentric osteolysis without nephropathy as have McManus *et al.*[23] and Omer and Mossman.[26] Our case also exhibits additional areas of osteolysis and thus involvement of bones other than the carpals does not differentiate MON from HMO.

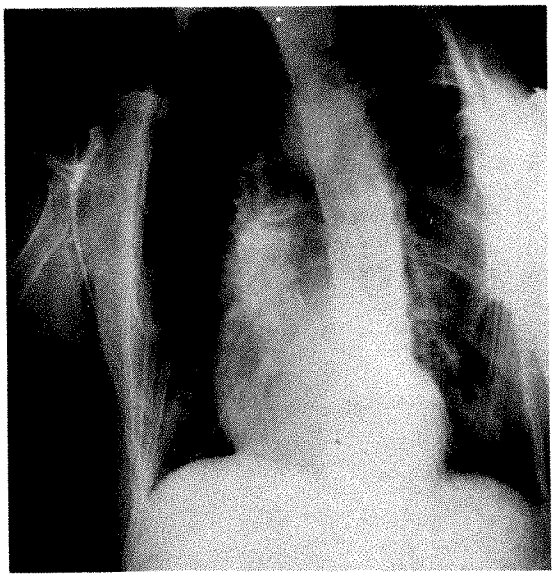

FIG. 6. A poorly positioned frontal chest roentgenogram reveals resorption of the right humeral head and distortion of the shoulder joint. The clavicles and ribs are demineralized and slightly thinned.

HEREDITARY MULTICENTRIC OSTEOLYSIS

There have been 23 cases of the dominant form of hereditary multicentric osteolysis (HMO) reported in detail.[3,4,9,13,23,25,26,29,31] Our case is the 24th case. There have been three cases of the recessive form of HMO,[32] for a total of 26. The details of these reports are summarized in Table II.

The dominant variety of HMO follows a characteristic clinical course. The onset is at the age of three to four years with arthritic complaints involving the wrists and ankles which may be exacerbated by mild trauma. This is followed by an asymptomatic period in adolescence during which varying amounts of disappearance of the carpal and tarsal bones occur. Progressive deformity develops in the third decade with complete dissolution of the involved bones. None of the hereditary cases has had significant renal disease.

The recessive variety of HMO described in three siblings by Torg *et al.*[32] has a clinical course relatively similar to the dominant form. They believe, however, that it can be roentgenographically differentiated from the dominant form: that, although there is carpal and tarsal osteolysis with relative sparing of the adjacent tubular bones in both varieties, there is an increase in caliber of the short tubular and long bones which is characteristic in the recessive form.

It should be noted that Shurtleff *et al.*[29] titled their paper "Hereditary Osteolysis with Hypertension and Nephropathy"; however, renal abnormality was observed only in the father who was 38 years of age at the time of the study. His age would be most unusual for the severe nephropathy seen in MON. Also, a subsequent report[9] could not substantiate Shurtleff's description of hypertension and nephritis. The other two extensively studied cases had no

Table I

MULTICENTRIC OSTEOLYSIS WITH NEPHROPATHY

Author	Age at Presentation	Presenting Symptoms	Presenting Roentgenographic Finding	Roentgenographic Change	Renal Function	Other
Marie *et al.*, 1951, 1956, 1963[18,19,20] Mahoudeau *et al.*, 1961[17]	5 years (F)	Stiff wrists; walking difficulties	Irregular distal radius	Disappearance of carpus and tarsus over 12 years Lysis and subluxation of elbows	Hypertension and azotemia, first noted age 21 years	Death from renal failure, age 22 years. Renal lesion resembles chronic glomerulonephritis. Additional costal and vertebral osteolysis. Club feet
Neyroud *et al.*, 1956[24] Lazier and Rutishauser, 1965[14]	20 months (M)	Pes planus, club hand, limitation of elbow movement; difficulty walking	Osteoporosis of tarsals	Disappearance of carpus and tarsus. Epiphyseal osteolysis of elbows. Resorption of distal ulnae and proximal metacarpals and metatarsals	Hypertensive nephropathy with uremia	Death from renal failure, age 18 years
Derot *et al.*, 1961[8]	18 years (F)	Wrist drop at 9 years	Right carpus half the size of left	Absence of right carpal bones with "sucked candy" appearance of proximal metacarpals	Hypertension and azotemia	Also had scoliosis and club feet. Lost to follow-up
Torg and Steel, 1968[33]	2½ years (F)	Swollen, painful wrists	Irregularity and demineralization of carpals at age 4 years	At age 9 years: absent carpals. Tapered metacarpals and distal radii and ulnae. Resorption at elbows. Lytic defects right tarsus	Albuminuria at 9 years	Pseudoarthrosis left clavicle. Forty year old father with mild hypertension and albuminuria but no skeletal deformity Patient was reported at age 9 years without subsequent report
Macpherson *et al.*, 1973[16]	2 years (M)	Deformity of wrists (noted during work-up for club feet)	Small irregular carpals; tapered metacarpals and ulnae; irregular elbows with dislocated radii	Striking progression at 14 years with additional resorption of tarsals	Abnormal urinalysis at 2 years	Two aunts with renal disease. Death from uremia age 14 years

TABLE II

HEREDITARY MULTICENTRIC OSTEOLYSIS (HMO)

Author	Age at Presentation	Presenting Symptoms	Presenting Roentgenographic Finding	Roentgenographic Change	Renal Function	Other
Omer and Mossman, 1958[26] McManus *et al.*, 1972[23]	4½ years (F)	Difficulty walking	26 years—absent carpals and demineralized tarsals	38 years further dissolution including metacarpals and distal radii and ulnae with ulnar deviation at wrist; minimal progression of tarsals	Normal blood urea nitrogen	Height 4 ft., 11 in.
	4 years (M) (son of above)	Wrist stiffness and deformity	No carpals visible; irregular tarsals	Progressive loss of carpals and adjacent tubular bones	Proteinuria noted at age 16 years (no known follow-up report)	Progressive osteolysis of right knee and right hip and left hip
Thieffry and Sorrel-Dejerine, 1958[31]	(1) 25 months (M) (son)	Deformed wrists with limited range of motion	Normal wrists at 16 months	25 months—absence of carpals and partial disappearance of tarsals	Normal	Follow-up to age 9 years
	(2) 3½ years (31 year old mother)	Arthritis of left wrist	Diminished ossification of left carpus with thin forearm			Follow-up to age 31 years
	(3) (grandmother)		Osteolysis of distal radii and proximal carpi			Died at age 56 years
	(4) 4 years (half sister of 1)	Short, thick wrists	Deformity of carpi			
	(5) 3 years (half brother of 1)		Irregularity of carpi and tarsi			
Normand, 1962[25]	1½ years (F)	Painful, swollen left wrist		Progressive disappearance of carpi with tapering of proximal metacarpi and shortening of ulnae	Normal urine at age 4 years	Biopsy left radius revealed no evidence of an inflammatory process. Limitation of motion of elbows. Follow-up to age 4 years
Shurtleff *et al.*, 1964[29]	(1) 3½ years (F)	Warm, tender wrists			Normal	Age 4 years, hypertension of 134/80. Marked inflammatory reaction after biopsy
	(2) 4 years (F) (sister of 1)	Rash followed by tender, swollen wrists	Small irregular carpal bones	Progressive osteolysis of carpi	Normal	Marked inflammatory reaction after biopsy
	(3) 3–4 years (father of 1 and 2; 38 years old at time of report)	Tender, swollen wrists		Progressive osteolysis of carpi and tarsi	Normal	Hypertension 200/110. Marked deformity left elbow ascribed to trauma
Coleman *et al.*, 1965[4]				Changes in carpals and associated joints and in distal radii		4 cases in one family (8 year old boy, his father, his paternal aunt, and the aunt's daughter)
Caffey, 1967[3]	(1) 6 years (F)	Painful, swollen wrists	Wrists and ankles normal	Irregular right carpus at age 7 years	Normal	Biopsy—normal maturation and mineralization. Normal cartilage with electron microscopy
Gluck and Miller, 1972[9]	(2) 4½ years (M) (brother of 1)	Painful, swollen wrists	Irregular carpi	Continued narrowing of carpus	Normal	Biopsy—same as 1
	(3) 5 years (grandfather of 1 and 2)	"Wrist symptoms"				Bilateral wrist deformities
	(4) (father of 1 and 2)					Similar to 3
Torg *et al.*, 1969[32]	(1) 5 years (M)	Deformity proximal interphalangeal joints right hand; right swollen ankle	Demineralization right tarsus; increased caliber of shafts of metacarpals and phalanges	Progressive resorption for tarsals and left carpus	Normal	Presumptive recessive transmission
	(2) 2 years (M) (brother of 1)	Deformity of hands and feet		Complete carpo-tarsal osteolysis, age 10 years and tarsal changes. Elbow resorption	Not reported	
	(3) 6 years (M) (brother of 1 and 2)	Painful, swollen wrists	Carpal osteolysis		Not reported	
Kohler *et al.*, 1973[13]	(1) 8½ years (M)	Wrist deformity	Osteolysis of carpi	Progressive lysis of carpi; tarsi "fused"	Normal	Follow-up to age 42 years
	(2) 6 years (M) (son of 1)	Occasional wrist and ankle stiffness	Osteolysis of right carpus	Progressive osteolysis of right wrist; lysis of left wrist at 13 years		Marfan-like appearance. Follow-up to age 17½ years
	(3) 5 years (M) (brother of 2)	Wrist and ankle stiffness	Osteolysis of carpi	Progressive osteolysis including ulnae	Not reported	Marfan-like appearance. Follow-up to age 16 years
	(4) 4 years (F) (sister of 2 and 3)	Painful, swollen left wrist	Irregular distal left radial epiphysis	Osteolysis of left carpus	Normal	Marfan-like appearance. Normal healing of pelvic fractures. Follow-up to age 15 years

significant renal disease. Thus, these cases appear to represent HMO rather than MON.

Normand's[25] case may be in either category. Follow-up was only to four years of age at which time the patient had a normal urinalysis; however, it is possible that this patient will develop nephropathy later in life and become an example of MON.

The oldest case of idiopathic multicentric osteolysis previously presented was 56 years of age.[31] The osseous changes in our case are much more extensive than in any previously reported case. This is probably due, at least in part, to continuation of the basic pathological process over a period of many years. Also, the patient's inability to walk has most likely contributed to bone loss because of disuse osteoporosis.

DIFFERENTIAL CONSIDERATIONS

Differential considerations certainly include some forms of arthritis. In fact, in a discussion of juvenile rheumatoid arthritis, Martel *et al.*[21] illustrate a case of progressive loss of the carpal bones between the ages of one and four years. In a communication to Macpherson and co-workers,[16] Martel admitted that this case may, indeed, be multicentric osteolysis rather than juvenile rheumatoid arthritis. Juvenile rheumatoid arthritis can be differentiated clinically from IMO by absence in the latter of acute phase reactants, clinical signs of systemic disease, and absence of inflammatory changes in biopsy specimens.

The Winchester syndrome can be differentiated both clinically and roentgenographically from IMO and, consequently, is considered to be a completely different disease which can lead to multiple areas of bone dissolution. It was first described by Winchester *et al.*[34] in 1969 as an acid mucopolysaccharidosis with skeletal deformities simulating rheumatoid arthritis. Subsequently, Hollister *et al.*[12] concluded that the Winchester syndrome should be classified as a nonlysosomal connective tissue disease. The distinguishing features of the Winchester syndrome are onset in infancy of arthralgia and joint stiffening with resulting deformities of the trunk and limbs. It appears to be inherited as an autosomal recessive.[34] The patients have coarsened facial features and peripheral corneal opacities. They are dwarfed and have progressive symmetric flexion contractures of the major and minor joints rendering them unable to ambulate. Carpo-tarsal osteolysis occurs but there are also generalized profound osteoporosis and other small joint destruction.[12] The type of destructive joint disease in Winchester syndrome suggests juvenile rheumatoid arthritis, although pain and deformity predominate over inflammation and heat. There is no fever or elevation of the erythrocyte sedimentation rate. In addition, roentgenograms show the phalanges expanded and coarsened.[34]

Aseptic necrosis resulting in partial or complete resorption of the carpals was thought to be a differential consideration by Caffey[3] who described his cases of IMO as "bilateral carpal necroses," but Gluck and Miller[9] provided more detailed information about Caffey's cases and designated them as "familial osteolysis of the carpal and tarsal bones." Differential points which exclude aseptic necrosis are its self-limited nature[29] and the fact that aseptic necrosis usually involves a single bone.

Another differential possibility is multicentric reticulohistiocytosis (lipoid dermato-arthritis).[2,15] This is a dermatologic disease which has an insidious onset in the fifth decade with the appearance of nontender, painless lumps in the skin of the extremities, trunk, face, and oral mucosa.[28] Arthritic complaints that resemble rheumatoid polyarthritis ensue. There are remissions and exacerbations for a period of about eight years.[7] Joint deformity occurs most frequently in the knees, shoulders, wrists, and hips. There is bone destruction with resorption of subarticular bone, especially of the distal interphalangeal joints of the hands and feet. The early changes can simulate gout or psoriatic arthritis.[28]

Franquois and Detrait[8] reported two

siblings with the triad of: "(1) a subepithelial central dystrophy of the cornea; (2) xanthomata of the skin; and (3) an osteochondral dystrophy localized in the distant parts of the extremities." The latter finding resembles carpo-tarsal osteolysis.[30] Arthrogryposis is a congenital condition characterized by multiple joint contractures[27] and conceivably could be a problem in roentgenographic differentiation.[25] There are flexion and ulnar deviations at the wrist. Fusion, rather than osteolysis, of the carpal bones subsequently occurs.

Many other entities have been mentioned in the differential diagnosis of IMO. These include post-traumatic regional osteolysis and ulceromutilating acropathy.[14] Macpherson *et al.*[16] consider renal osteodystrophy as a possible differential in MON. The generalized skeletal changes distinguish renal osteodystrophy. Also, in renal osteodystrophy the skeletal changes are preceded by renal disease but in MON both appear at about the same time.

PATHOGENESIS

The etiology of IMO is unknown. The roentgen and clinical features of both HMO and MON indicate a similar pathogenetic mechanism. Proliferation of synovial arterioles has been found in IMO,[29] but there is no indication of hemangiomatosis[14,29,32] as is evident in Gorham's disease.[10] Local trauma which has been thought to be incidental in Gorham's disease[29] has occasionally been reported in IMO.[9,13]

The familial occurrence of HMO is consistent with a hereditable defect which could cause an immunologic abnormality. The involvement of two organ systems in MON suggests a pathogenetic mechanism similar to Goodpasture's syndrome. In Goodpasture's syndrome one type of antibody reacts with autologous antigens of the capillary basement membranes of both the pulmonary alveoli and the renal glomeruli.[1] The renal lesion is a proliferative glomerulonephritis.[1] The fact that renal and skeletal involvement occur simultaneously in most cases of MON[16] supports a Goodpasture-like pathogenesis. Antibodies could be reacting to autologous renal and osseous antigens. Biopsy specimens in MON also have revealed renal vascular changes similar to the periarticular tissue changes seen in a wrist biopsy.[29]

The questionable association of trauma is possibly significant. Minor wrist trauma, either direct or from increased usage, might cause sufficient tissue injury to uncover antigens to which the body could then react. Cross-reactivity of similar renal antigens would then produce pathological changes in both the kidneys and the bones. We are not aware of studies attempting to identify a definite tissue immune mechanism for this syndrome. One report[14] did not find immunoelectrophoretic evidence of an immunological abnormality.

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MYOSITIS OSSIFICANS CIRCUMSCRIPTA: A BENIGN LESION WITH A MALIGNANT DIFFERENTIAL DIAGNOSIS*

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ABSTRACT:

Localized areas of active myositis ossificans, occurring without a clear history of antecedent trauma, have been referred to as a "pseudo-malignant osseous tumor of soft tissue." This lesion may be mistaken both roentgenographically and pathologically for a malignancy. The roentgenographic signs which favor a diagnosis of non-neoplastic heterotopic bone formation include a lucent zone between the lesion and the adjacent bone, an intact underlying cortex, diaphyseal location, dense calcification in the periphery, and loss of volume on serial films.

NON-NEOPLASTIC heterotopic bone formation may result from a single major episode of trauma, or repetitive minor trauma. There is also a certain number of patients with this lesion from whom no history of trauma can be elicited. Those localized areas of myositis ossificans circumscripta, without antecedent injury, have been referred to in the literature as the "pseudo-malignant osseous tumor of soft tissue." The correct roentgenographic diagnosis is especially significant since these patients present clinically with a tender soft tissue mass, and biopsies may be mistakenly interpreted as a malignant lesion.[1,3–5]

Five cases of "pseudo-malignant osseous tumor of soft tissue" are presented here, with emphasis on the roentgen signs which differentiate this lesion from a soft tissue or parosteal sarcoma.

REPORT OF CASES

CASE I. This eleven year old female was admitted with a presumptive diagnosis of malignant tumor of the right shoulder. One month prior to admission, the patient noted pain and swelling in the right shoulder. The past medical history was non-contributory. Physical examination was unremarkable except for a fullness in the region of the right shoulder. The patient had previously experienced local tenderness there, but it had resolved by the time of the hospital admission. The serum alkaline phosphatase level was 13.2 King-Armostrong units. A roentgenogram (Fig. 1*A*) revealed a calcified mass adjacent to the scapula, with periosteal new bone formation along the lateral aspect of the scapula. Tomography (Fig. 1*B*) demonstrated the densest calcification in the periphery of the lesion. Microscopic examination of a biopsy specimen revealed sheets of spindle cells interspersed with spicules of mature osteoid. The area of myositis ossificans was then locally resected (Fig. 1, *C–F*).

CASE II. A 24 year old female presented with a one year history of a non-tender mass in the right index finger. Growth of the lesion had been slow but progressive. The past medical history was unremarkable. Physical examination revealed an immobile mass lesion, lateral to the second metacarpophalangeal joint, associated with swelling of the surrounding soft tissues. The serum alkaline phosphatase level was 3.3 King-Armstrong units. The roentgenograms (Fig. 2, *A* and *B*) demonstrated a soft tissue mass, with partial calcification of its periphery. A periosteal reaction was noted along the adjacent bone, but the cortex of the phalanx was intact. At operation, the tumor was described as firm, well demarcated, and of cartilaginous

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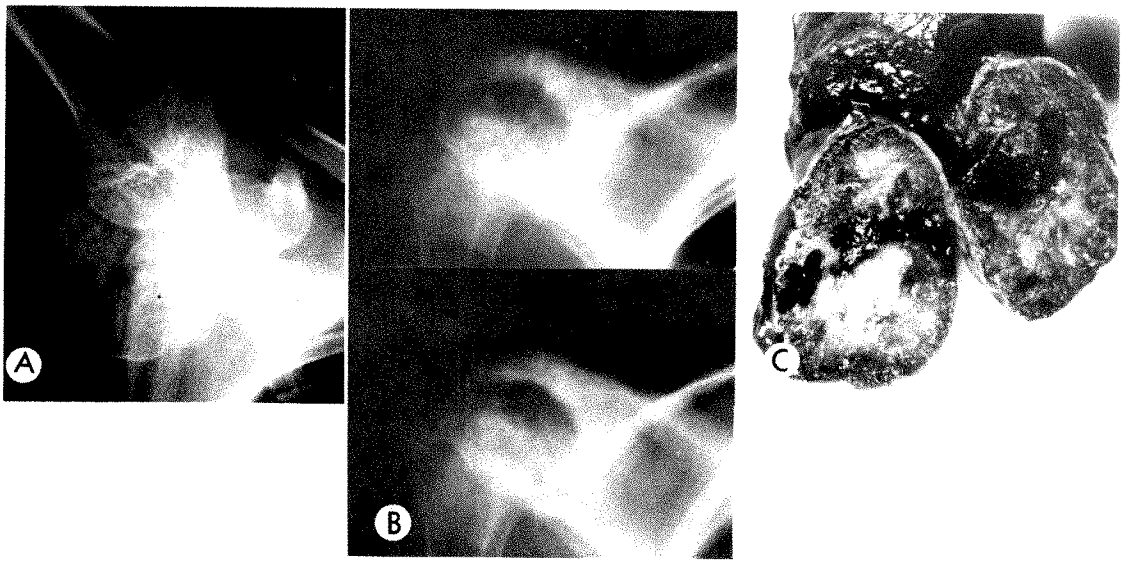

Fig. 1. Case i. Eleven year old female with myositis ossificans circumscripta. (*A*) Roentgenogram demonstrating a calcified soft tissue mass. (*B*) Tomograms confirming that the lesion was most densely calcified in its periphery. (*C*) The well encapsulated surgical specimen, with a hemorrhagic center, and bone in the periphery.

consistency. The surgical specimen measured 2.5×2 cm and was fixed to the adjacent bone. The pathologic diagnosis on the initial biopsies was a malignant sarcoma. Further histologic material obtained from the amputation specimen revealed the tumor to be a "pseudomalignant osseous tumor of soft tissue."

Case iii. This twelve year old female presented with a chief complaint of a mass in the left groin, which was discovered incidentally five weeks prior to admission. The history failed to reveal any previous trauma to the area. Physical examination demonstrated a hard, non-tender mass in the left inguinal region,

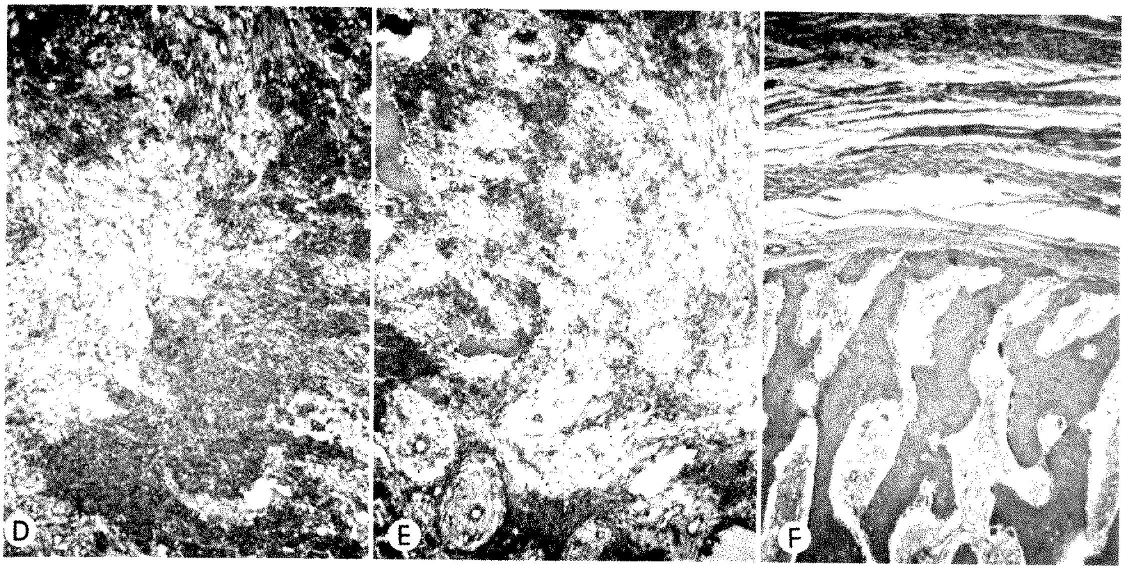

Fig. 1. (*D*) A microscopic section from the inner zone of the mass demonstrating hemorrhage, necrosis, and fibroblasts. (*E*) The middle zone, containing osteoblasts and immature bone. (*F*) The outer zone, or periphery of the lesion, which is composed of mature trabeculae.

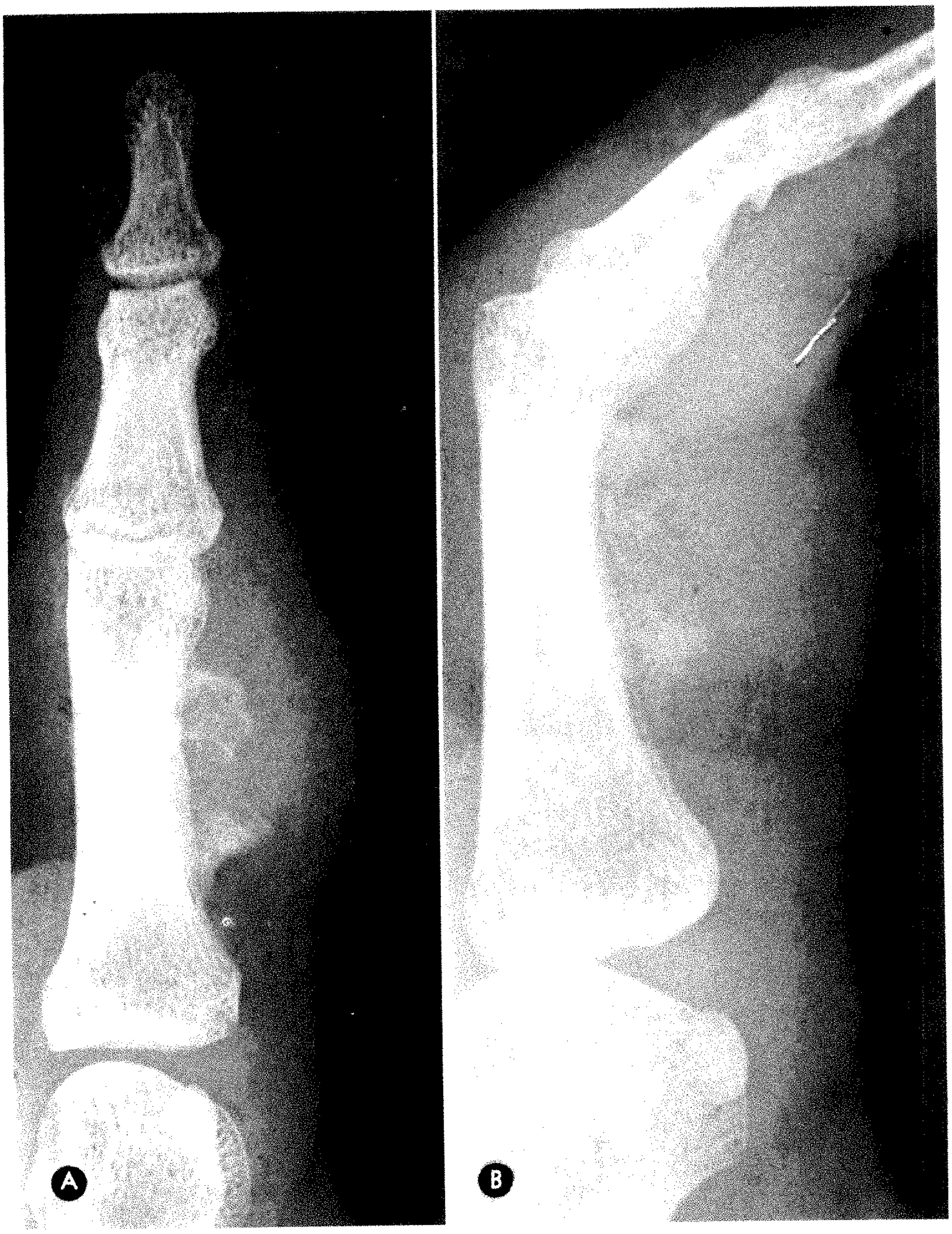

FIG. 2. Case II. (*A* and *B*) Roentgenograms of a 24 year old female, with a calcified soft tissue mass adjacent to the middle phalanx of the right index finger. The densest calcification is noted peripherally in the upper and lower poles of the lesion, and a lucent zone persists between the lesion and the adjacent cortex. The lesion was surgically proved to be myositis ossificans circumscripta.

associated with limitation of hip flexion. The alkaline phosphatase level was 15.3 King-Armstrong units. The roentgenogram (Fig. 3*A*) revealed a calcified mass below the inferior pubic ramus, with the densest calcifications in the periphery. The underlying osseous structures were intact. An angiogram (Fig. 3*B*) demonstrated increased vascularity in the region of the tumor but no evidence of abnormal vessels or arteriovenous shunting. At surgery, a firm mass was dissected from the fascia of the adductor muscles. The operative specimen (Fig. 3*C*) was of bony consistency, and measured 7.6×6 cm. The histologic examination showed aggregates of osteoblasts and bony spicules in all stages of maturation. Intact skeletal muscle fibers were also found within the lesion.

Case iv. A 50 year old female presented with a chief complaint of swelling of the left arm of two months' duration. The area was initially tender, but over a period of time it became painless. The past medical history was non-contributory. Physical examination revealed a ten centimeter indurated area on the anterior aspect of the left arm. The serum alkaline phosphatase level was 5.5 King-Armstrong units. Roentgenograms (Fig. 4, *A* and *B*) of the humerus demonstrated a calcified soft tissue mass adjacent to the shaft of the bone, which on multiple projections was seen to be separated from the osseous structures by a lucent zone. At surgery, a 7×3.5 centimeter mass was removed (Fig. 4*C*). Microscopically, the center of the tumor consisted of whorls of spindle cells. However, the periphery was composed of mature osseous tissue within a fibrous stroma.

Case v. A 15 year old male was admitted with a chief complaint of pain in the left hip

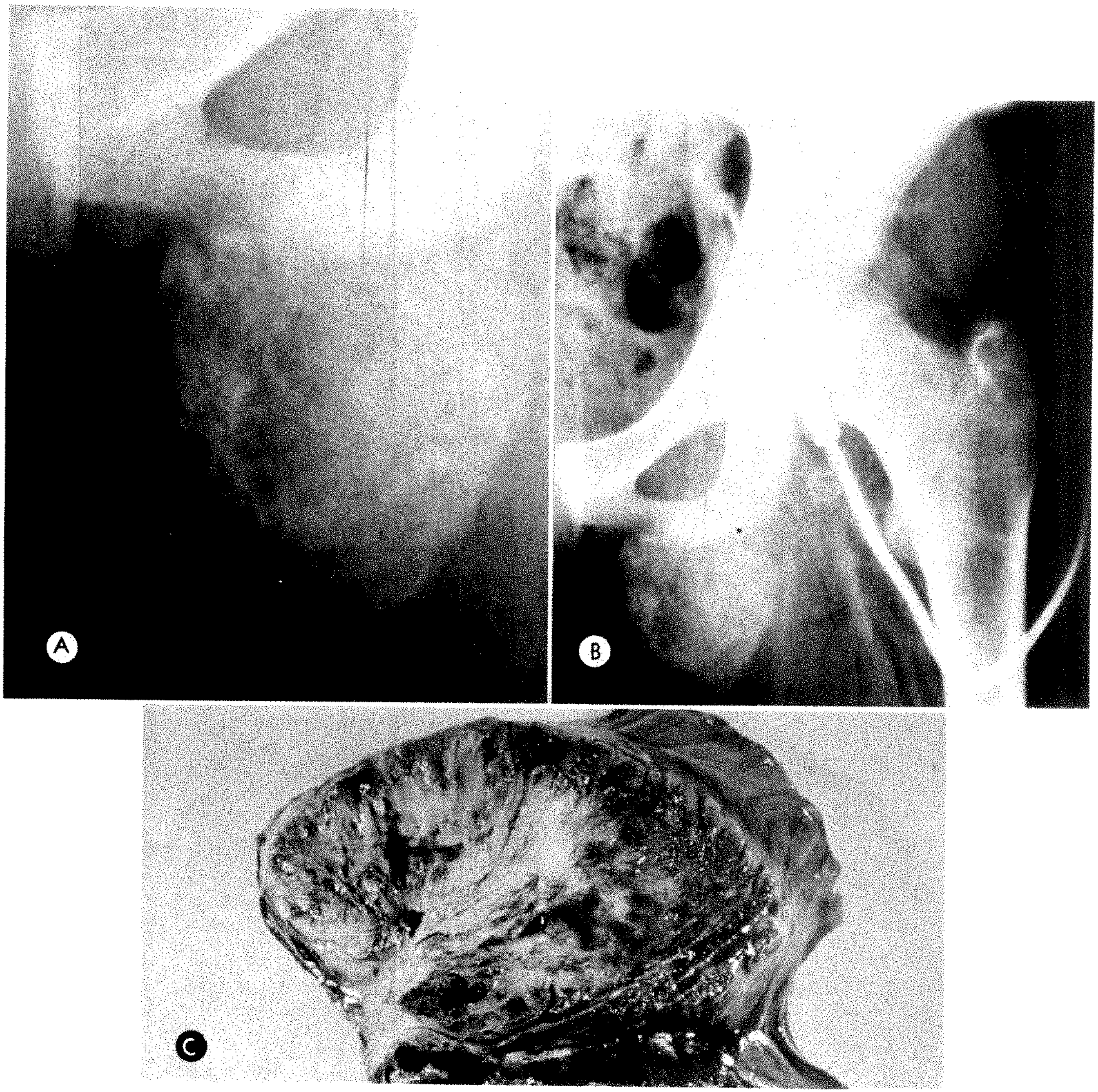

Fig. 3. Case iii. (*A*) Roentgenogram of a twelve year old female with an area of myositis ossificans adjacent to the left ischium and pubis. (*B*) An angiogram demonstrated increased vascularity but no specific signs of malignancy. (*C*) The surgical specimen.

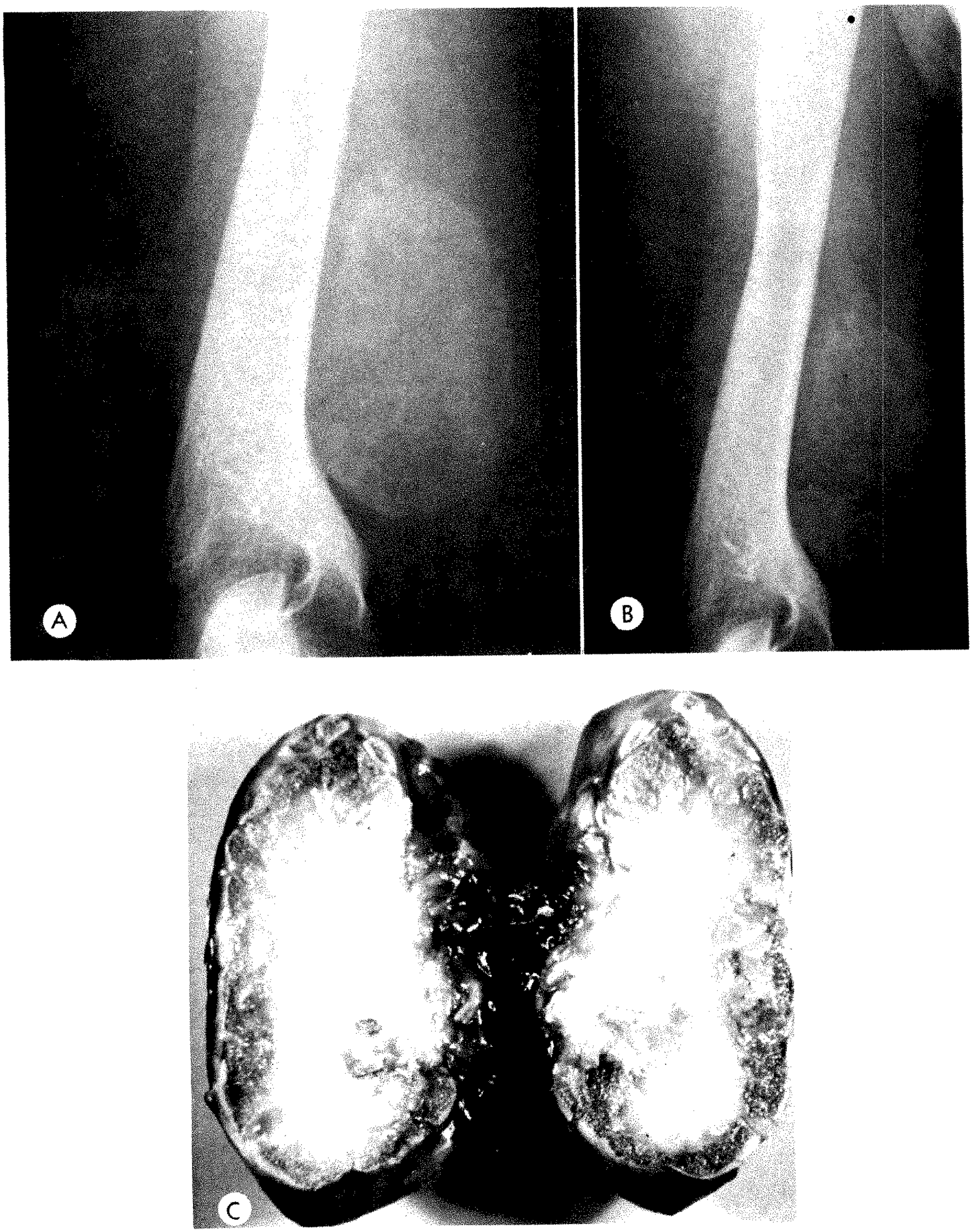

FIG. 4. Case IV. (*A* and *B*) Roentgenographic studies of a 50 year old female demonstrating a calcified area of myositis ossificans in the left arm. A lucent zone separates the lesion from the adjacent bone, the humerus is normal, the lesion is diaphyseal in location, and the densest calcification is in the periphery. (*C*) The gross surgical specim[illegible]

of two months' duration. There was a questionable history of having experienced a "pulled muscle" several months prior to the onset of pain. Physical examination revealed a nontender mass just below the left inguinal ligament. The serum alkaline phosphatase level was 233 milliunits/milliter. The roentgenograms (Fig. 5, *A* and *B*) demonstrated an ossified mass adjacent to the superior margin of the left acetabulum. At surgery, the tumor was observed to have a fibrous capsule and was adherent to the soft tissues and the iliac crest. The hip joint was not involved. The gross specimen measured 5.5×2.8 centimeters. On histologic examination there was a central zone of cellular stroma, but more peripherally, bony trabeculae were noted. The pathologic diagnosis was myositis ossificans circumscripta.

DISCUSSION

Sixty[12] to seventy-five[13] percent of large series of myositis ossificans circumscripta have a clearly traumatic origin. The remaining patients either suffer from one of the systemic problems associated with soft tissue ossification (paraplegia, poliomyelitis, burns, tetanus), or apparently develop the lesion spontaneously. Those localized lesions, presenting without a history of antecedent trauma, were first recognized as a distinct entity in 1956 by Fine and Stout.[4] These authors reviewed 16 ossifying tumors of soft tissue; twelve proved to be extraosseous osteosarcomas, but four behaved benignly, with long term survivals. The clinically non-aggressive tumors were well circumscribed, and specimens demonstrated mature bone in the periphery. On the basis of the pathologic characteristics they called the benign lesions "pseudo-malignant osseous tumors of soft tissue."[4] In 1958, Ackerman[1] reported five similar cases of non-neoplastic heterotopic bone formation, without a clearly traumatic origin. Both Ackerman[1] and Jeffreys and Stiles[10] included these lesions in the general category of myositis ossificans.

Most areas of non-neoplastic heterotopic bone formation arise in the large muscle groups of the thighs and upper arms, in close proximity to the shaft of a bone. The

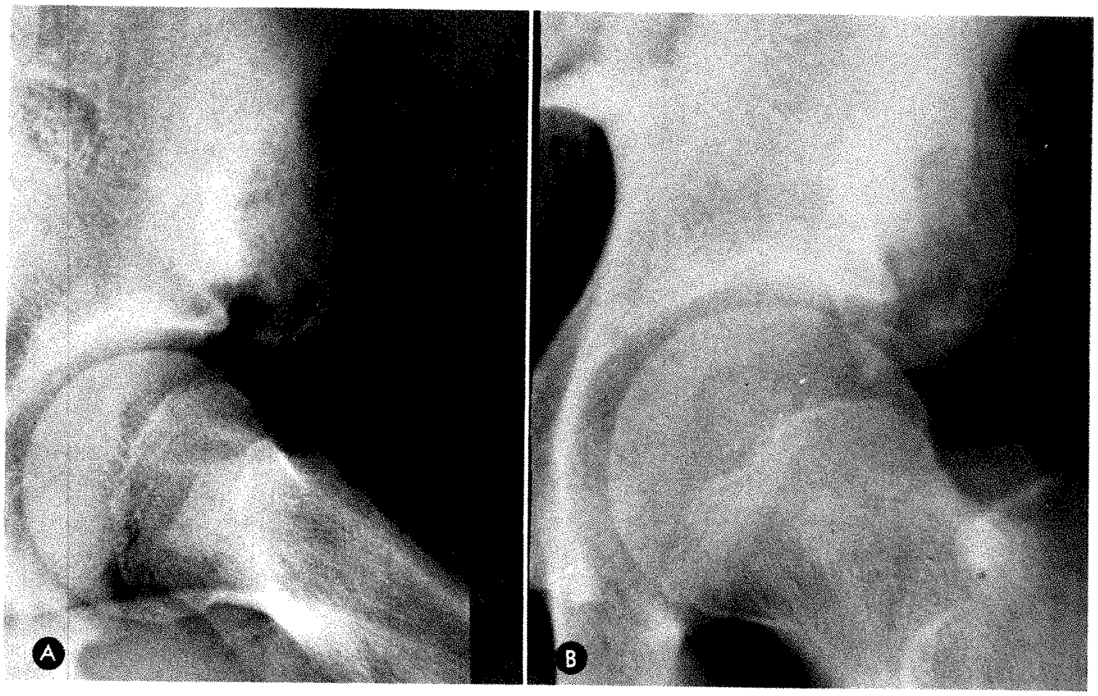

Fig. 5. Case v. (*A* and *B*) Roentgenograms of a 15 year old male with an area of myositis ossificans circumscripta adjacent to the superior aspect of the acetabulum.

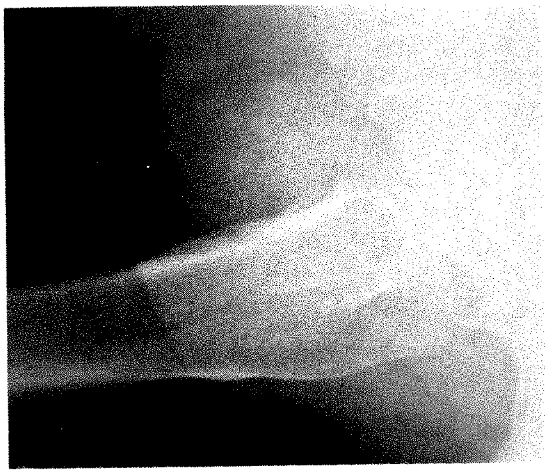

FIG. 6. Calcified synovial tumor.

major roentgen and pathologic differential diagnoses of the active phase of myositis ossificans are parosteal osteosarcomas, extra-osseous osteosarcomas, and synovial sarcomas. The last is included since one-third of synovial tumors calcify, and they may arise in the intramuscular spaces at some distance from a joint[14] (Fig. 6).

Recognition of the benign character of myositis ossificans is imperative in order to avoid mutilating surgery. Clinical information may be useful, although not diagnostic in distinguishing the benign ossifying tumors of soft tissue from malignancies. Patients with myositis ossificans circumscripta tend to be adolescents or young adults (four of the five cases described here were less than 30 years of age), whereas those with extra-osseous osteosarcomas are usually in the sixth decade of life.[4] The pain associated with non-neoplastic heterotopic bone formation is most severe early in the course of the lesion, and gradually diminishes, a pattern which is not characteristic of malignancies. An elevated serum alkaline phosphatase level is not significant since this value may be abnormal in the presence of either benign (Cases I; III; and IV) or malignant bone forming tumors. Although trauma may not be the only etiology of myositis ossificans circumscripta,[3] at least some of the so-called "spontaneous" areas are the result of soft tissue injury, which patients do not associate with the word "trauma," *e.g.*, minor injury or a sustained form of irritation.[5–7] Gilmer and Anderson[7] referred to this type of injury as "inferential trauma." The location of the lesion in Case V indicates that its etiology was probably related to an avulsion of the rectus femoris. However, even if careful questioning does elicit a history of antecedent trauma, it does not establish the benignity of a particular lesion. In a series of 16 cases of parosteal osteosarcomas, six patients recalled trauma to the area in question.[15]

The pathologic criteria establishing the diagnosis of myositis ossificans circumscripta are based on this lesion's characteristic pattern of maturation. Several unanswered questions remain concerning the initial events in the histogenesis of non-neoplastic heterotopic bone formation, including: (1) the mechanism by which soft tissue injury stimulates localized bone formation;[5] (2) the source of the osteoblasts and whether they originate from damaged periosteum or pleuripotent cells already present in the connective tissue;[5,11] and (3) the target of injury. Several investigators postulate that the title "myositis" is incorrect, and that it is damage to the interstitium which produces soft tissue ossification.[1,2] Although the initiation of the process may be imperfectly understood, the microscopic changes which ensue have been well documented. Mesenchymal proliferation results in the production of focal masses of collagen, which are capable of accepting the deposition of calcium salts. Once the heterotopic osteoblasts begin producing matrix, the lesion becomes grossly defined and develops a fibrous capsule, separating it from the surrounding tissues (Fig. 1*C*). Microscopically, the developing lesion demonstrates three zones. This zone phenomenon, which was described by Ackerman,[1] is an important criterion for the diagnosis of myositis ossificans since no such divisions occur in sarcomatous lesions. The center of the lesion (Fig. 1*D*) is occupied by rapidly proliferating fibroblasts, with areas of hemorrhage and necrotic muscle. The middle zone (Fig. 1*E*) contains osteoblasts with islands of immature bone. In the presence of the florid osteoblastic activity, the functioning cells may appear young and hyperchromatic. If the central and middle zones alone are biopsied, a pathologic differentiation from sarcoma may be difficult. The third and most peripheral zone (Fig. 1*F*), is composed of mature trabeculae, which are clearly separated from the surrounding connective tissue. Thus, maturation proceeds in a centrifugal fashion, with the central area being the last to ossify. The pathologic criteria which differentiate immature myositis ossificans circumscripta from a sarcoma are: (1) the zone phenomenon; (2) lack of invasion of the adjacent tissues; and (3) the inclusion of viable muscle fibers, which would be destroyed by an advancing tumor. Eventually, the entire area of myositis ossificans is transformed into mature bone, with the formation of a cortex and marrow space.

The appearance of myositis ossificans circumscripta on serial roentgenograms reflects the pathologic maturation of the lesion. Initially, there is soft tissue swelling, with or without periosteal reaction. This then proceeds to flocculated calcification, which is finally replaced by mature heterotopic bone. The roentgen findings in the first four weeks depend on the precise localization of the initial insult. Gilmer and Anderson[7] have classified the circumscripta form of myositis ossificans into three categories, on a primarily topographic basis. The first group are the extra-osseous lesions, which arise within the substance of a muscle and are not in continuity with the adjacent bone. These cases will show only soft tissue swelling on early roentgenographic examinations. The second type are the periosteal lesions, which result from direct damage to the cambium, and within the first two weeks produce a layered or sunburst periosteal reaction. In the past, the latter group has also been referred to as ossifying subperiosteal hematomas[7] or periostomas.[9] The third category of cases, arising in the immediate proximity of a bone, are characterized as parosteal myositis ossificans. They are also frequently associated with an early periosteal reaction. The early roentgenographic findings, like the early pathologic findings, are non-specific, and diagnosis is extremely difficult.

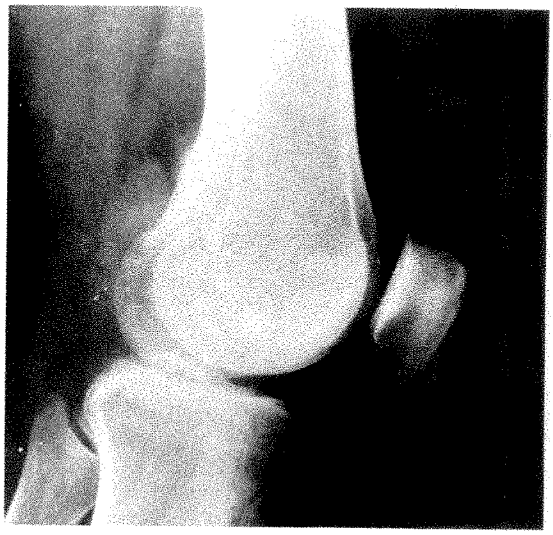

Fig. 7. Parosteal osteosarcoma. There is no lucent zone separating the mass from the underlying bone, and the densest calcification is in the base of the lesion.

Approximately one month after the insult to the soft tissue, flocculated calcifications can be recognized on roentgenograms, although, their time of appearance can vary from eleven days to six weeks. The calcific densities gradually enlarge and coalesce, and the centrifugal maturation of the lesion can be observed roentgenographically. The roentgenographic criteria for the diagnosis of active myositis ossificans include a lucent zone between the lesion and the underlying bone, seen on at least one of multiple projections. Parosteal osteosarcomas may appear to have a similar lucent zone, but the separation is incomplete: a pedicle extends from the tumor to the normal bone. A second finding which suggests that the lesion is benign is that the cortex is intact, even in the presence of periosteal new bone formation. Thirdly, myositis ossificans circumscripta is usually located adjacent to the shaft of a bone, as opposed to sarcomatous lesions which are usually metaphyseal in origin. Lastly, the zone phenomenon is also reflected on roentgenograms and, as a result, the densest calcification occurs in the periphery of the lesions. In malignant bone-forming tumors, the densest matrix is formed at the base of the lesion, where the cells are better differentiated (Fig. 7). The zone phenomenon can be modified by muscular forces and the lesion may appear cylindrical as opposed to round, or the calcification may be denser at one pole, where maturation has proceeded further[7] (Case II). If the lesion is oval, its long axis is parallel to the shaft of the bone.[13] Serial roentgenograms may also be helpful, since myositis ossificans circumscripta shrinks as it matures, and a "lacy" pattern of new bone can be distinguished from calcification.[12] The application of angiography to differentiate the active phase of myositis ossificans circumscripta from malignant bone-forming tumors has not been well investigated. One reported case and the one patient studied by this modality in our series both showed hypervascularity but no evidence of amputated vessels, venous lakes, or arteriovenous shunting.

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LESIONS RESEMBLING GOUT IN PATIENTS WITH RHEUMATOID ARTHRITIS*

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ABSTRACT:

Although roentgenographic appearances are seldom important in establishing the diagnosis of rheumatoid arthritis or gout, atypical appearances of individual lesions may confuse the distinction between these two conditions. Sixteen patients with rheumatoid arthritis were selected to illustrate joint and soft tissue lesions which resemble gout. The lesions are divided into five broad categories on the basis of the appearance and sites of bone erosion as well as the nature of soft tissue changes. Symmetrical bilateral joint involvement was found to be especially helpful in distinguishing rheumatoid arthritis from gout.

THE typical roentgenologic appearances of rheumatoid arthritis and gout have been well described.[2] The pattern of bone erosion in the hands, wrists, and feet in rheumatoid arthritis is characteristic.[3,5] The appearances of erosions themselves, their sites, and the nature of associated soft-tissue swelling can usually be distinguished from those seen in gout. In some cases, however, the roentgenographic appearance of individual lesions in rheumatoid arthritis may mimic those of gout and confuse the diagnosis.

The purpose of the paper is to document those lesions of rheumatoid arthritis which may resemble gout, to describe these lesions, to review the characteristic roentgenologic appearances of rheumatoid arthritis, and to emphasize the most reliable roentgenographic features for distinguishing rheumatoid arthritis from gout.

MATERIAL AND METHOD

Sixteen patients with rheumatoid arthritis whose roentgenograms showed changes resembling gout were chosen for review. In all but one patient, the clinical diagnosis of rheumatoid arthritis was never in doubt. Twelve patients had normal serum uric acid levels. Uric acid levels were not estimated in four patients. Serum latex tests were positive in ten patients, negative in three, and not done in two; in one patient the diagnosis of rheumatoid arthritis was confirmed at another hospital after removal of a rheumatoid nodule from the lung.

RESULTS

Five types of lesions were found which might confuse the differential diagnosis between gout and rheumatoid arthritis.

1. *Subarticular erosions.* Erosions with well-defined margins were seen in the metatarsal heads in six patients (Fig. 1) and interphalangeal joints of the great toes in four patients with or without accompanying soft tissue swelling. Two patients had similar erosions in the first interphalangeal joints accompanied by localized soft-tissue swelling on one aspect of the joint.

Subarticular erosions with sclerotic margins (corticated erosions) were accompanied by marked fusiform swelling around the third proximal interphalangeal (PIP) joint and localized soft-tissue swelling in the second, third, and fourth PIP joints (Fig. 2).

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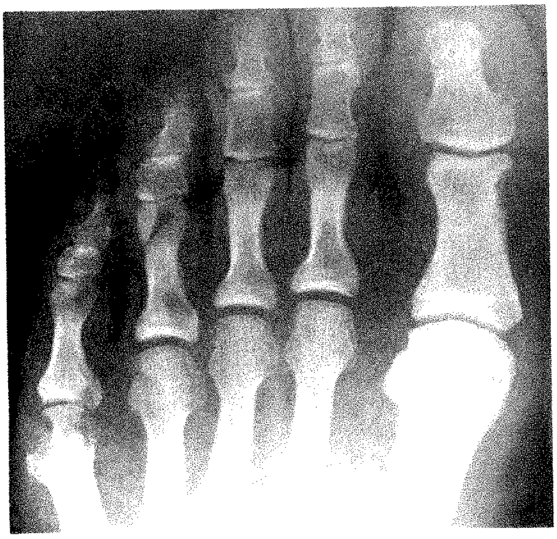

FIG. 1. Right foot: sclerotic, well-defined margins with subarticular erosions in the fifth metatarsal head and the first proximal phalanx.

II. *Erosion or scalloping of diaphyses.* Erosions and fusiform soft-tissue swelling similar to those described above were seen in the diaphysis on the volar and lateral aspects of the third and fourth finger proximal phalanges. These erosions were also accompanied by localized soft-tissue swellings (Fig. 3). Multiple contiguous erosions were sometimes present along the diaphysis (Fig. 4).

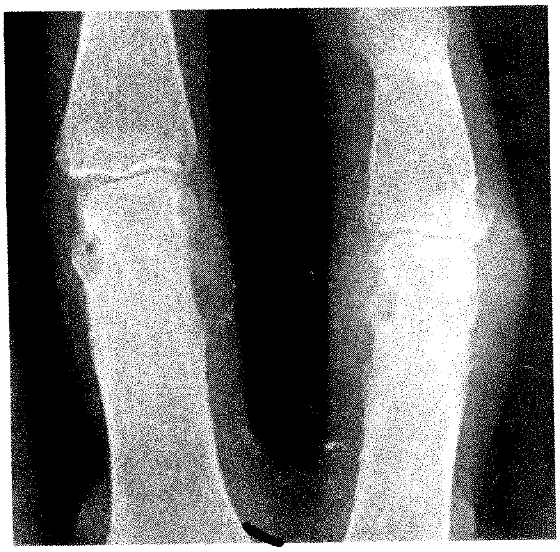

FIG. 2. Right third and fourth fingers: subarticular erosions with localized area of swelling.

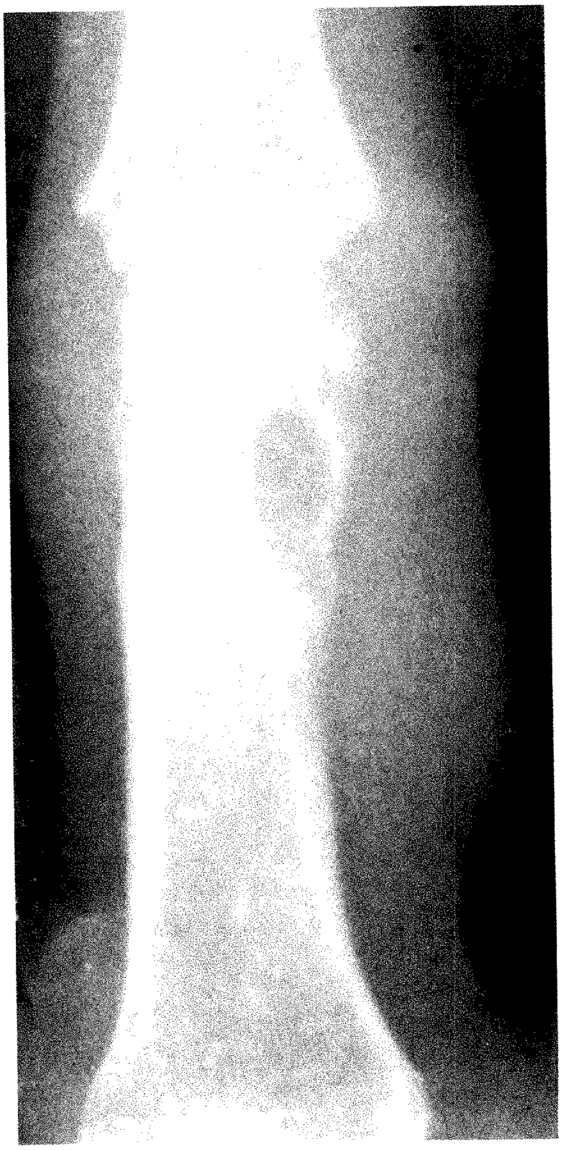

FIG. 3. Right middle finger: erosion on the volar and radial aspects of the proximal phalanx with accompanying localized soft-tissue swelling.

A large localized swelling with accompanying cortical scalloping was seen in the distal end of the radius in one patient. This scalloping of the cortex of the radius differed from that seen in the proximal phalanges: the edges of the erosion did not subtend an acute angle with the normal cortex but merged gradually into its contour (Fig. 5).

III. *Destruction of cartilage and hyper-*

trophic bone. Hypertrophic bone, presumably formed in an attempt at repair after cartilage and bone damage, produced an appearance similar to the overhanging edge of bone seen in gout in two patients. One lesion was in the second metacarpophalangeal joint; the second was in the proximal interphalangeal joint of the fifth toe (Fig. 6) without localized soft-tissue swelling.

iv. *Localized or discrete soft-tissue swellings.* Two patients had marginal erosions sometimes seen in gout in the second and third finger PIP joints of both hands. They were accompanied by localized and discrete soft-tissue swellings which made the appearances more suggestive of gout.

v. *Soft tissue lesions.* Localized soft tissue lesions resembling a tophus were seen in three patients. They were found adjacent to a normal ulnar styloid, alongside the radial styloid and wrist, and on the volar aspect of the proximal phalanges of several fingers. In another patient a similar lesion was seen adjacent to the base of the fifth metatarsal of the right foot (Fig. 7).

DISCUSSION

In rheumatoid arthritis typical soft-tissue swelling is fusiform and surrounds all aspects of the joint. The types of erosions have been described and classified according to their appearances and clinical sites:[5]

1. Marginal erosions, which are usually poorly defined and without sclerotic borders, occur within the joint capsule in an area of bone devoid of cartilage. These so-called bare areas are lined by a double layer of synovium (*i.e.*, at synovial reflections). A sclerotic border, when present, indicates healing.

2. Compression erosion, produced by the mechanical effect of impaction, is usually seen in the metacarpophalangeal joints.

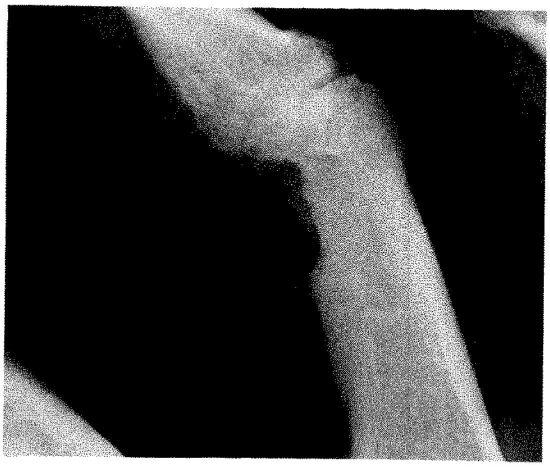

Fig. 4. Right middle finger, oblique view: two adjacent erosions on the volar and lateral aspects of the proximal phalanx produce a scalloped appearance.

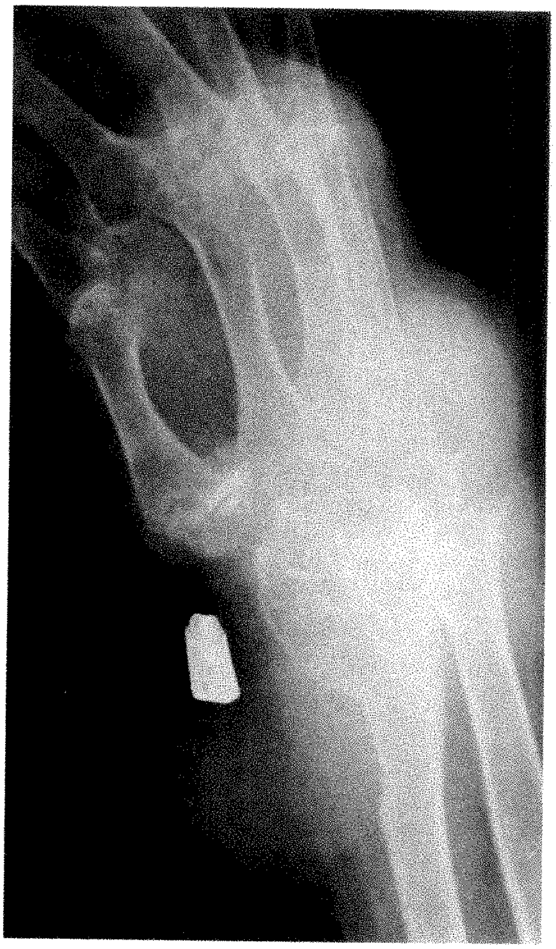

Fig. 5. Left hand and wrist: large soft tissue masses, probably nodular synovial proliferation. Note the discrete nature of the mass over the distal end of the radius (its margins subtend an acute angle with the radial cortex) and the pressure erosion of the bone. There is typical rheumatoid destruction of the wrist and the metacarpophalangeal joints.

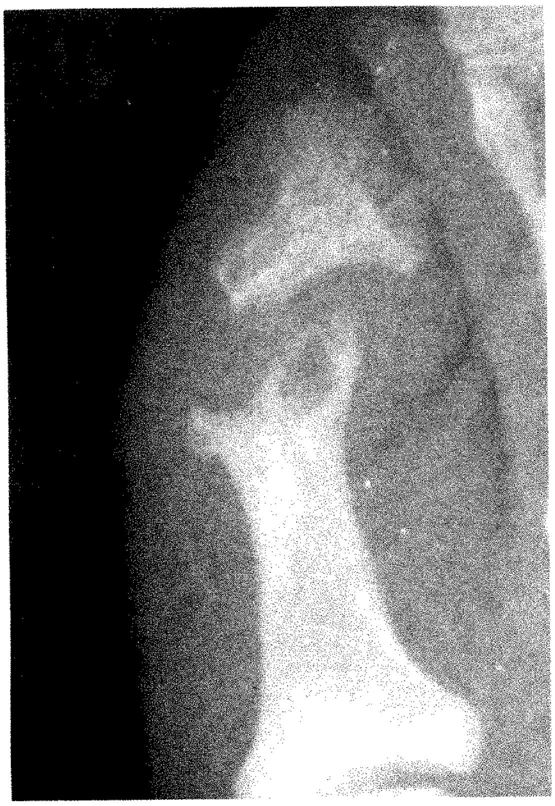

FIG. 6. The proximal interphalangeal joint of the fifth toe is destroyed. Hypertrophic bone has formed and projects laterally from the proximal phalanx, simulating an overhanging edge.

3. Superficial surface resorption is a subtle finding which resembles the subperiosteal resorption seen in hyperparathyroidism. It is visible either on the dorsal aspect of the first metacarpal or the first proximal phalanx.

4. Pseudocyst formation may be an erosion projected *en face* or a truly subarticular cyst. The latter are thought to result from extrusions of synovial fluid through minute cracks in articular cartilage; subsequent pressure leads to erosion of the underlying spongiosa and endosteal cortex.

Gout erosions also have characteristic but not firmly diagnostic appearances.[2,4] They are either sharply marginated or discrete subarticular punched-out lesions often quite remote from the joint margin. A ledge of new bone is formed around the tophus from the edge of its accompanying erosion in 40 percent of patients with tophaceous gout.[4] This overhanging edge is thought to represent new bone laid down in an attempt at repair and is relatively uncommon in rheumatoid arthritis. A tophus usually appears as a discrete soft tissue mass, the margins of which tend to form a sharp angle with the adjacent bone. They often contain calcium, which is frequently faint and poorly defined on the roentgenogram.

Individual corticated subarticular or marginal erosions, especially when asso-

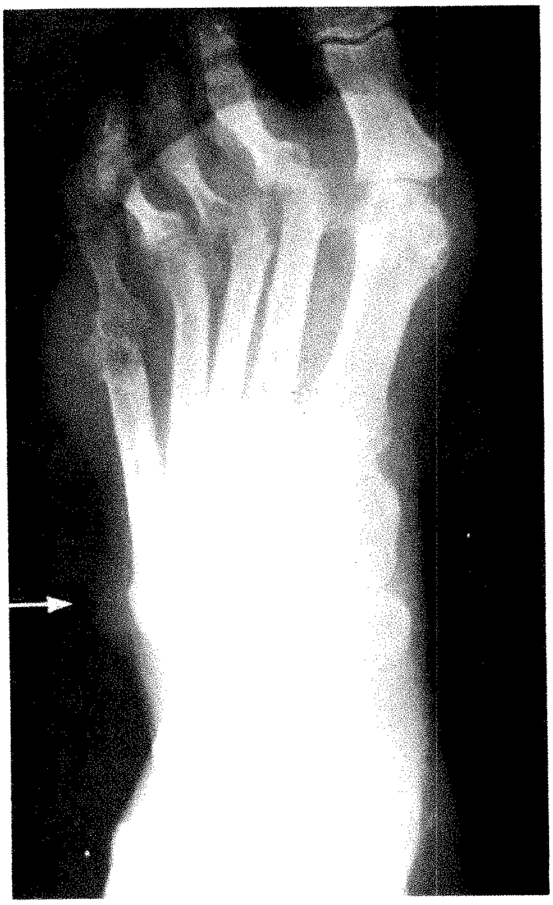

FIG. 7. Note discrete soft tissue masses over the base of the fifth metatarsal and metacarpophalangeal joint. Destruction and deep corticated subarticular erosion of the fifth metacarpophalangeal joint together with the discrete soft tissue mass suggest gout, and aspiration biopsy was recommended. There was also bilateral symmetry of joint involvement characteristic of rheumatoid arthritis.

ciated with asymmetrical soft-tissue swelling, may be seen in gout. The erosions on the lateral and volar aspects of proximal phalanges are very unusual lesions in rheumatoid arthritis and certainly are highly suggestive of gout when associated with localized nodular soft-tissue swellings. Indeed, marked bony destruction with a sclerotic margin and associated discrete soft tissue mass in the head of the fifth metatarsal so resembled gout that we recommended biopsy (Fig. 7). Cholesterol crystals which may form in patients with rheumatoid arthritis were obtained from the needle aspiration. No urate crystals were found.

The classical overhanging edge of gout was simulated in another patient but the same joint in the opposite foot was involved. These appearances represented a healed erosion with excessive hypertrophic bone.

Localized soft-tissue swelling may reach considerable size; it represents nodular synovial proliferation[3] and resembles gouty tophi. The margins do not form sharp angles with the adjacent bone but tend to merge gradually into the normal soft tissue contour. The localized synovial proliferation was adjacent to the radius in one patient (Fig. 5), however, and produced a large localized discrete mass with borders that formed sharp angles with the adjacent bone. This mass produced scalloping in the cortex of the radius, almost certainly a pressure effect.

Similar bony appearances have been reported in the proximal ulna and olecranon process in relation to subcutaneous rheumatoid nodules.[1] Previously when high doses of vitamin D were used in the treatment of rheumatoid arthritis, these masses were known to calcify.[3] When associated with erosion, as occurs in the proximal phalanges, the resemblance to gout is more striking.

In all the cases reviewed there was a pattern of symmetry of joint involvement. In the very early stages of rheumatoid arthritis asymmetrical joint involvement may be present, but with progress the pattern of symmetrical involvement becomes obvious.[3] Certainly, at a time when joint damage is sufficient to produce lesions which resemble gout, the pattern of symmetrical involvement should be present. We therefore feel that when individual joint lesions resemble gout, the presence of bilateral, symmetrical joint involvement should lead to a confident diagnosis of rheumatoid arthritis and avoid confusion.

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BRONCHOPULMONARY FOREGUT MALFORMATIONS*

A UNIFYING ETIOLOGICAL CONCEPT

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ABSTRACT:

Two cases of congenital bronchopulmonary foregut malformation are reported and another 27 cases reviewed and the findings analyzed. The left lower lobe and the entire right lung are the most common locations of pulmonary involvement. The distal portion of the esophagus or cardioesophageal junction was the most common site of communication (83 percent). The majority of the patients (60 percent) presented in the first eight months of life, and the incidence in females was nearly twice that in males.

Chronic cough, recurrent pneumonias and respiratory distress were the most common clinical findings, whereas two patients were totally asymptomatic.

The esophagogram was the single most useful diagnostic procedure (82 percent). The microscopic structure of the congenital fistula resembled esophagus, bronchus or both. Surgical treatment was curative in most instances. Some deaths occurred prior to corrective surgery, whereas the postoperative deaths in most instances were related to severe associated congenital anomalies.

We believe a common embryologic pathogenesis leads to the formation of a variety of bronchopulmonary foregut malformations. These bronchopulmonary foregut malformations include intralobar and extralobar sequestrations, pulmonary sequestration with patent, or involuted—partial or complete—gastroesophageal communication, esophageal or gastric diverticula, and esophageal or bronchogenic duplication cysts.

PATENT, congenital communications between accessory lung tissue and esophagus or stomach are extremely rare and only 24 such instances are recorded in the literature.[1–4,7,9,10,12–14,16,17,20–26,29,35,37,38] The purpose of this article is not only to report two such patients we recently had a chance to examine, but also to emphasize that this rare anomaly provides evidence for an interesting and plausible theory of common pathogenesis of the gamut of bronchopulmonary foregut malformations (BPFM) including intralobar and extralobar sequestrations with or without communication with the alimentary tract, foregut duplication cysts, and esophageal diverticula.

REPORT OF CASES

CASE I. B.K., a ten week old male infant, was admitted to St. Paul Children's Hospital with a history of slow weight gain, intermittent low grade fever and chronic cough since birth. The cough was initially productive of stringy mucoid material but currently was hacking and nonproductive. The cough frequently led to gagging and emesis. The child fed poorly and slowly. The feedings did not produce any coughing or gagging episodes.

The physical examination revealed a pale, irritable, dyspneic infant weighing 4 kg, temperature 37.6° C, pulse 160/min, respiration 72/min; the blood pressure was not recorded. Breath sounds over the right hemithorax were decreased but no rales nor rhonchi could be

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From the Children's Hospitals in Minneapolis, and St. Paul, Minnesota, and Oakland, California.

heard. A grade 2/6 systolic ejection murmur, heard best at the apex, radiated to the back. Electrocardiography showed biventricular hypertrophy. The liver and spleen were palpable 4 cm below the costal margins.

A chest roentgenogram (Fig. 1) demonstrated almost complete opacification of the right hemithorax with the exception of a triangular segment at the base of the right lung. Multiple, small, round radiolucencies were scattered throughout this opacity. An esophagogram (Fig. 2*A*) demonstrated a large, esophagobronchial fistula extending from the proximal esoph-

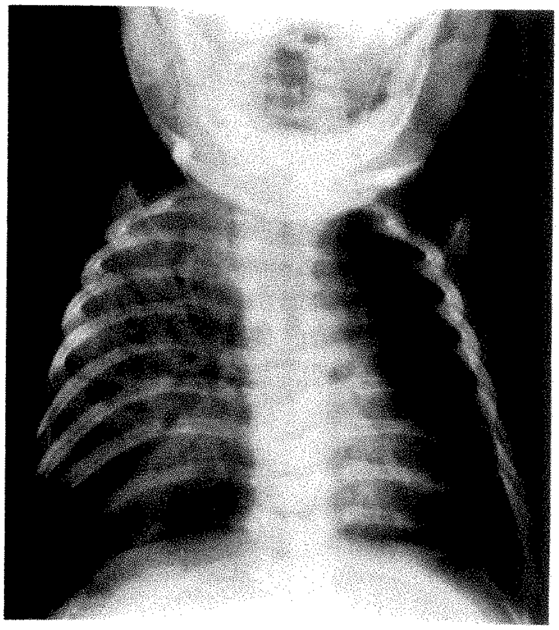

Fig. 1. Case 1. Chest roentgenogram. Frontal view demonstrating almost complete opacification of the right hemithorax with the exception of a small segment at the right costophrenic angle. Multiple air bronchograms are seen throughout this opacity.

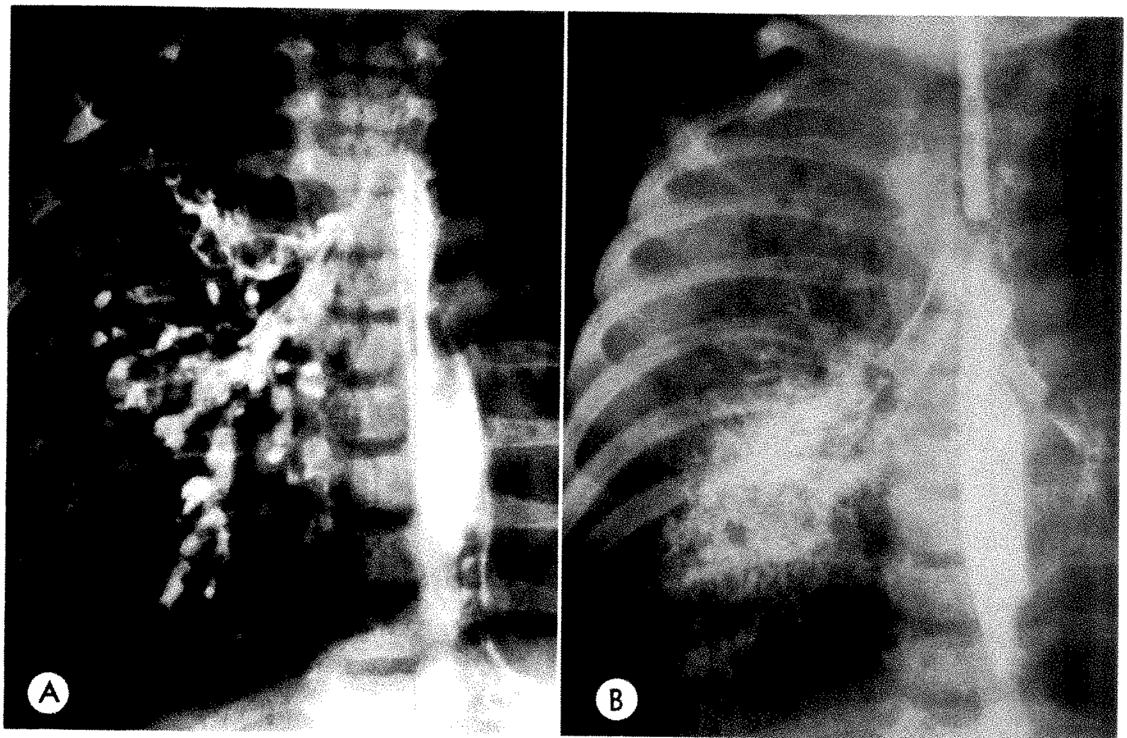

Fig. 2. Case 1. (*A*) Esophagogram. A large esophagobronchial fistula extends from the proximal esophagus at T3–T4 level to a large bronchus supplying the opaque portion in the right hemithorax. Moderately advanced cylindrical and saccular bronchiectasis is present. (*B*) Bronchogram. A bronchus supplies a small portion of the right lower lung. This bronchus did not communicate with, and was distinctly separate from the bronchus seen on the esophagogram. A fair amount of contrast medium has alveolarized, and no bronchiectasis is seen.

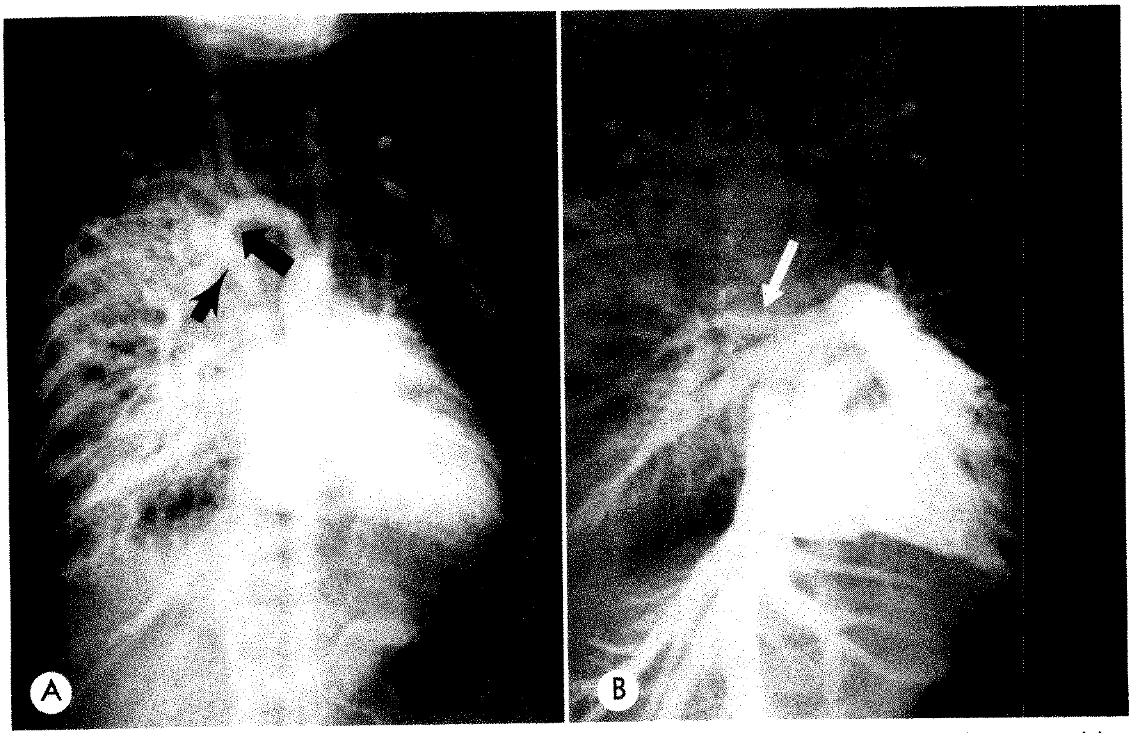

Fig. 3. Case 1. (*A*) Levogram phase following right atrial injection. A large aberrant systemic artery arising from the innominate artery at its division into the right common carotid and subclavian arteries supplies the BPFM (large arrow). BPFM drains into the azygos vein which leads to its dense opacification (small arrow). (*B*) Pulmonary arteriogram following right atrial injection. A small branch of the right pulmonary artery supplies the BPFM (arrow). The other branch of the right pulmonary artery supplies the normal right lung which is compressed in the medial and basilar portion of the right hemithorax.

agus at the T 3–4 level to a large bronchus on the right side supplying the opaque portion in the right hemithorax. Moderately advanced cylindrical and saccular bronchiectasis was observed in this bronchial segment. Since no opacification of the trachea and the bronchus supplying the aerated portion of the right lung was observed, a bronchogram was performed. This demonstrated a very small bronchus on the right side supplying the right lower lung field. This bronchus did not communicate with and was distinctly separate from the bronchus seen on the esophagogram and was free of bronchiectasis (Fig. 2*B*). The bronchogram also revealed a normal trachea and left bronchial system.

A levoangiocardiogram demonstrated a large aberrant vessel arising from the innominate artery at its division into the right common carotid and subclavian arteries (Fig. 3*A*). This vessel and a small branch of the right pulmo-

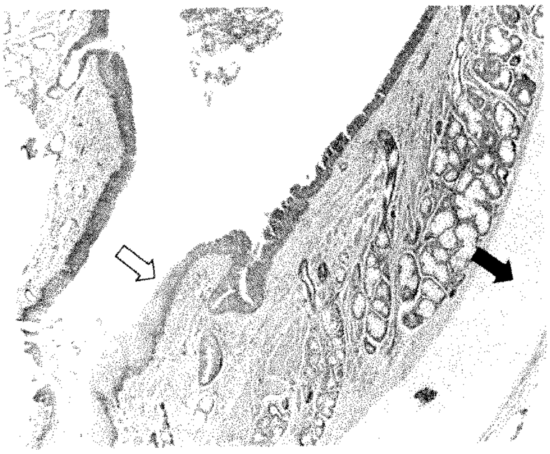

Fig. 4. Case 1. Microscopic findings of the fistulous tract. Hollow arrow showing transition of the esophageal stratified squamous epithelium into brush bordered pseudostratified ciliated columnar epithelium of the respiratory tract. Dark arrow indicates a large ring of hyaline cartilage.

nary artery (Fig. 3*B*) supplied the large bronchopulmonary foregut malformation. The draining veins entered into a large common vein which then drained into the dilated azygos vein.

At surgery, the malformation consisted of two, dark consolidated lobes with a separate pleural investment from the remaining normal lung. The smaller of these two lobes occupied the apical portion of the chest cavity and extended laterally and anteriorly, while the larger lobe occupied the entire posteromedial aspect of the right hemithorax. The normal lung, consisting of at least two separate lobes, was crowded into an inferior and anteromedial section and expanded immediately to fill the entire right hemithorax upon resection of the malformation. The esophagobronchial fistula was 1.5 cm in length and 0.5 cm in diameter. Microscopically the fistula resembled esophagus at the esophageal end, whereas at the bronchial end it resembled bronchus (Fig. 4).

Case 11. B.G.D. was admitted to Children's Hospital Medical Center in Oakland at the age of three days with exstrophy of the urinary bladder and ruptured omphalocele. After surgical correction of the omphalocele, the infant developed severe respiratory distress and died.

A chest roentgenogram on the day of birth showed the right hemithorax densely opacified with a single air bronchogram at the right base. The heart and mediastinal shadows were displaced to the right side. There was an unexplained opacity in the medial basal portion of the left hemithorax simulating the cardiac image. Several segmentation anomalies of the vertebral column were seen, along with fusion of the right first with second, and third with fourth ribs (Fig. 5*A*). Injection of gastrografin into the proximal esophagus showed an abnormal fistulous tract arising from the right side of the gastroesophageal junction and branching into both the right hemithorax and the opacity

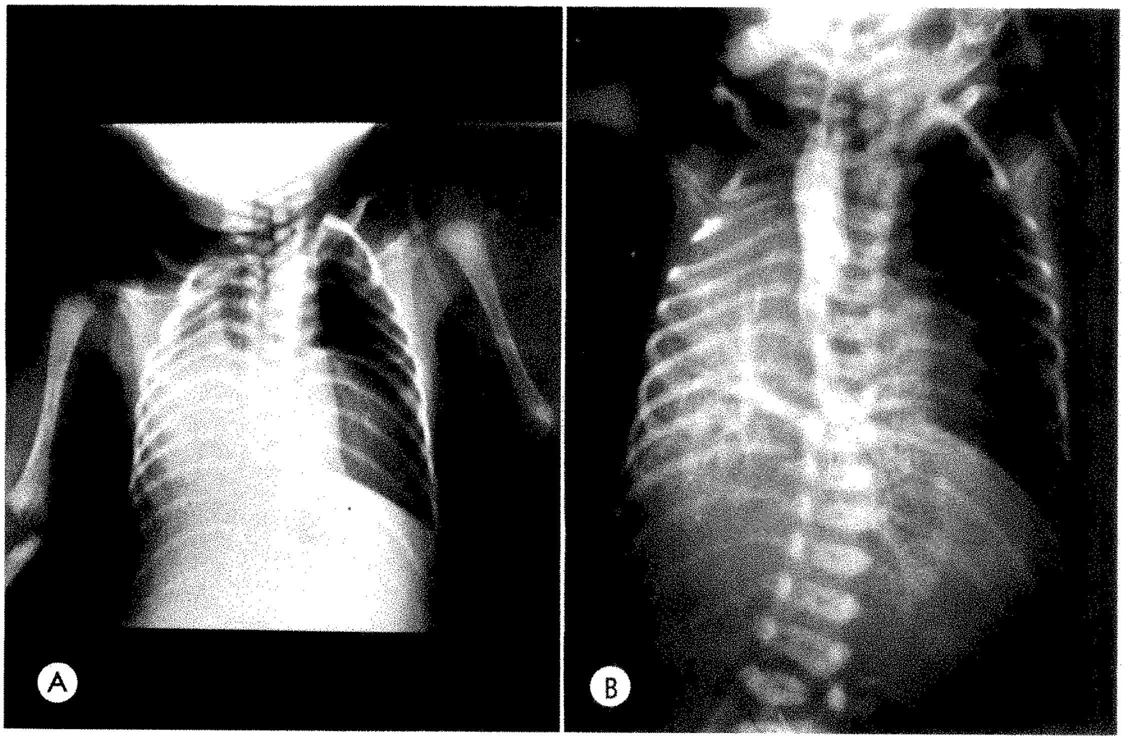

Fig. 5. Case 11. (*A*) Frontal view on the day of birth showing opaque right hemithorax with the exception of a small air bronchogram at the right base. Heart and mediastinal structures are shifted to the right side, with an unexplained opacity in the medial basilar portion of the left hemithorax. (*B*) Injection of gastrografin in the proximal esophagus. An abnormal fistulous tract arises from the right side of the distal segment of the esophagus and then branches into the right hemithorax and basilar portion of the left hemithorax. Hemivertebrae in the cervical, thoracic, and the upper lumbar spine along with congenital bridging of the first four ribs on the right side are seen.

in the basilar portion of the left hemithorax (Fig. 5*B*). The infant, in addition, showed duplication of the colon.

DISCUSSION

Twenty-six instances of bronchopulmonary foregut malformations with patent gastroesophageal communication have been recorded, including the present report. One of the authors (S.M.S.) has examined three more patients from Children's Hospital of Pittsburgh who are being reported as a part of a separate article.[36] Their clinical and roentgenologic findings are included here for the completeness of the statistical analysis.

Pulmonary Involvement (Table I). In ten of the 29 cases, the entire right lung was involved; in one stillborn infant, both right and left lungs were totally sequestered. The left lower lobe was involved in eleven, right lower lobe in four, both right lower lobe and left lower lobe in one, left upper lobe in one, and our first patient was the only one to have right upper lobe involvement.

Site of Gastrointestinal Communication (Table II). The lower esophagus or cardioesophageal junction was by far the most common site of communication—24 of 29 cases. The fundus of the stomach communicated in three instances. In one, it involved the mid-esophagus, while in our first case, the upper portion of the esophagus communicated with BPFM.

TABLE I

Pulmonary Involvement	Number of Patients
Entire right lung	10
Left lower lobe	11
Right lower lobe	4
Both lungs	1
Right and left lower lobes	1
Left upper lobe	1
Right upper lobe*	1

* Case 1.

TABLE II

Site of Communication	Number of Patients
Lower esophagus and cardio-esophageal junction	24
Fundus of stomach	3
Mid-esophagus	1
Upper esophagus*	1

* Case 1.

TABLE III

Age	Number of Patients
0–8 months	16
8 months to 18 years	6
More than 18 years	5

TABLE IV

Sex	Number
Females	15
Males	9
Not known	5

Age (Table III). Age at the time diagnosis is recorded in 27 cases, the other two being anatomic specimens. Sixteen of these have presented with clinical symptoms in the first eight months of life. Five of the seven patients who had symptoms in the first week of life had involvement of the entire right lung; the symptoms in these patients were often related to other severe congenital anomalies. Six other patients presented with clinical signs and symptoms in the pediatric group (18 years), whereas the remaining five presented in adult life (18 to 48 years).

Sex (Table IV). The incidence in females was nearly twice that in males. Fifteen patients were female, whereas nine were male. In five reported cases, sex was not recorded.

Clinical Signs and Symptoms. Chronic cough, often related to feeding, recurrent pneumonias, and respiratory distress were the most common clinical signs and symptoms. Infrequent findings were regurgitation of food, hemoptysis, and anemia. The infants having other congenital anomalies had clinical signs and symptoms related to those anomalies. Only two patients were asymptomatic.

Blood Supply. The arterial supply was from the abdominal aorta in nine; from the pulmonary artery in eight; and the thoracic aorta in five. Single examples of innominate, left gastric, and left adrenal artery supply to a BPFM were recorded. Our first case was the only patient to have both systemic (innominate) and pulmonary artery supply to a BPFM simultaneously. Venous drainage was pulmonary in eleven and systemic in ten.

DIAGNOSIS

An Esophagogram was the most useful diagnostic investigation. Of the 22 instances where the esophagogram was performed, the examination was diagnostic in 18.

Bronchography was performed in seven cases and was not diagnostic in any. In three, bronchiectasis was seen, while in four, displacement of the normal bronchi was observed.

Preoperative Angiography was performed in only three patients. It is, however, to be recommended as an aid to diagnosis and as a valuable guide in planning surgery, as it shows the number, caliber, and location of abnormal vessels, lessening the possibility of hemorrhagic complications due to inadvertent damage to them at surgery.

PATHOLOGIC STUDIES

Microscopic Structure of the Fistula. Microscopic findings have been recorded in 18 patients. In eight, transition of the esophageal structure into a bronchial structure was observed. In four, the mucosal lining was stratified squamous epithelium, whereas in five, bronchial stratified ciliated columnar epithelium was seen. In one, gastric mucosa lined the fistulous tract.

Associated Anomalies. Vertebral, gastrointestinal, genitourinary, and cardiac congenital anomalies were frequently associated with BPFM. Nine of the eleven patients with total involvement of the right lung, and ten of the 18 other patients with lobar involvement showed other congenital anomalies. These anomalies tended to be more varied and severe in those patients with total sequestration of the right lung. The most frequent anomalies were diaphragmatic hernia (five), vertebral and rib anomalies (six), and congenital heart lesions (four). In all five instances, the diaphragmatic hernia was on the left side and was associated with left lower lobe esophagobronchial communication. In four of the six cases in which vertebral and rib anomalies were observed, the entire right lung was involved. Other significant but rare anomalies were esophageal atresia and tracheo-esophageal fistula, duodenal stenosis, duplication of the colon, omphalocele, annular pancreas, posterior urethral valves, cleft palate, and Turner's syndrome.

Follow-up and Mortality Figures. Twenty-two patients had resection of BPFM: 16 are alive and doing well. Five postoperative deaths were directly attributable to associated severe congenital anomalies. One died four months following successful surgery due to respiratory tract infection. Three infants died prior to surgery.

ETIOLOGY AND EMBRYOGENESIS

No unanimity of opinion exists with regard to the origin of pulmonary sequestrations. Several theories have been discussed at length in the literature,[5,6,8,11,14,18,30,32,34] and these have been well summarized in some of the recent articles.[14,18,32] Most of these theories postulate that extralobar and intralobar sequestrations are two entirely different entities, but current evidence indicates that the two overlap considerably, and share a common embryogenesis.[14,16]

Normally, at five weeks of embryonic age (Fig. 6) a small lung bud develops from the ventral wall of the pharynx. This lung bud goes on to form a laryngotracheal tube which bifurcates into two primitive lung buds by seven weeks. Simultaneously a lateral furrow appears on each side of the laryngotracheal ridge. The furrows become progressively deeper and extend craniad to

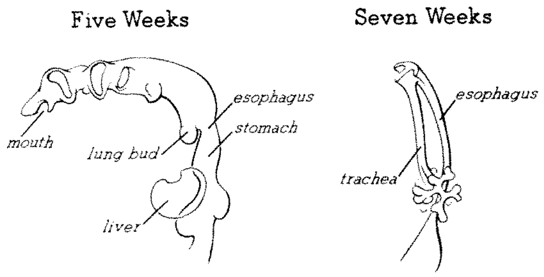

FIG. 6. Normal lung development.

join eventually, thereby separating the ventral laryngotracheal tube from the dorsal esophagus.

The theory which most adequately explains the embryogenesis of foregut malformations is that of a supernumerary lung bud which arises caudal to the normal location of a lung bud and migrates caudally along with the growing esophagus. If this accessory lung bud arises early in embryonic life before the development of the pleura, it is invested in adjacent normal lung, and becomes an intralobar sequestration. On the other hand, if this accessory lung bud develops later, when the pleura has already formed, it grows separate from the adjacent lung, becomes invested with its own pleura, and forms an extralobar sequestion. Thus, it is timing and not a qualitative difference in embryogenesis which determines whether a sequestration is intralobar or extralobar.

Intralobar and extralobar sequestrations have been said to have distinct characteristics.[34] In fact, in our cases as well as those previously described there is such tremendous overlap of these so-called classical characteristics that one may not reasonably try to distinguish between intra- and extralobar sequestation on the basis of blood supply, venous drainage, location, etc. Several cases of simultaneously occurring intra- and extralobar sequestrations have been reported.[18,27,28]

In those patients in whom the embryologic pedicle does not involute, the sequestration remains in free communication with the gastrointestinal tract through a muscular, epithelial lined tube—thus forming the type of BPFM under discussion (Fig. 7). The isolation of most cases of bronchopulmonary foregut malformations from the gastrointestinal tract can be attributed to involution of the embryologic pedicle. Such a hypothesis is given great credence by the discovery of intermediate stages of this involutionary process in which the sequestration is connected to the gastrointestinal tract by a fibrous strand. Examples of these incomplete forms, which most clearly indicate the genesis of these malformations, have been reported.[5,16,18] A variety of foregut malformations such as duplication or diverticula has been found in association with a sequestration and occasionally a gastric or esophageal diverticulum has been found to be incorporated within the fibrotic pedicle.[2,6] Complete involution of the stalk results in simple sequestration, which may be associated with a small notch on the outer wall of the esophagus at the site of prior embryonic communication.

A more complicated and embryologically interesting malformation occurs when sequestration co-exists with other foregut anomalies, such as ectopic pancreas, foregut duplication cysts, and gastroesophageal diverticula. The diverticula may arise either from the esophagus or from the fundus of the stomach like an epiphrenic diverticulum.[6,14,15]

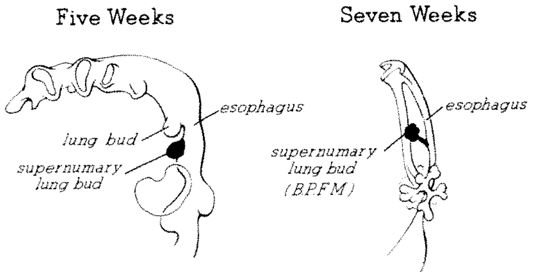

FIG. 7. Bronchopulmonary foregut malformation.

Figure 8, *A* and *B*, demonstrates a small bronchopulmonary foregut malformation of the right lower lung attached to the right lateral margin of the esophagus by a thin membranous stalk. A small vein and artery are present within this stalk along with a small esophageal duplication cyst.

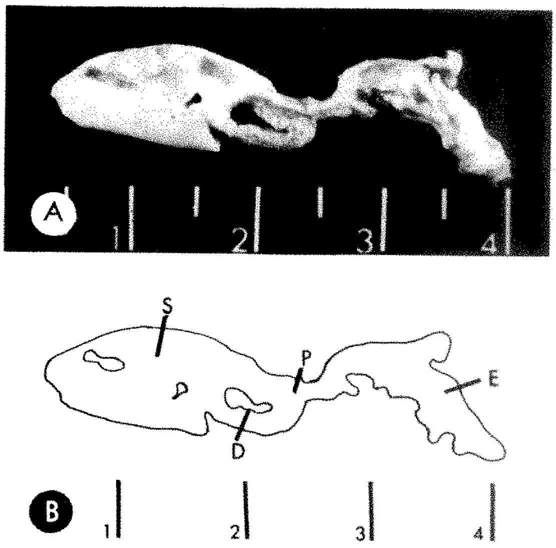

Fig. 8. (*A*) Gross specimen and (*B*) line drawing. An extralobar pulmonary sequestration (S), attached to the right lateral margin of the esophagus (E) by a thin membranous pedicle (P), which contained a small vein and artery and a small esophageal duplication (D) are demonstrated. This duplication communicated with the bronchus of the sequestration. (Courtesy of Dr. R. Telander.)

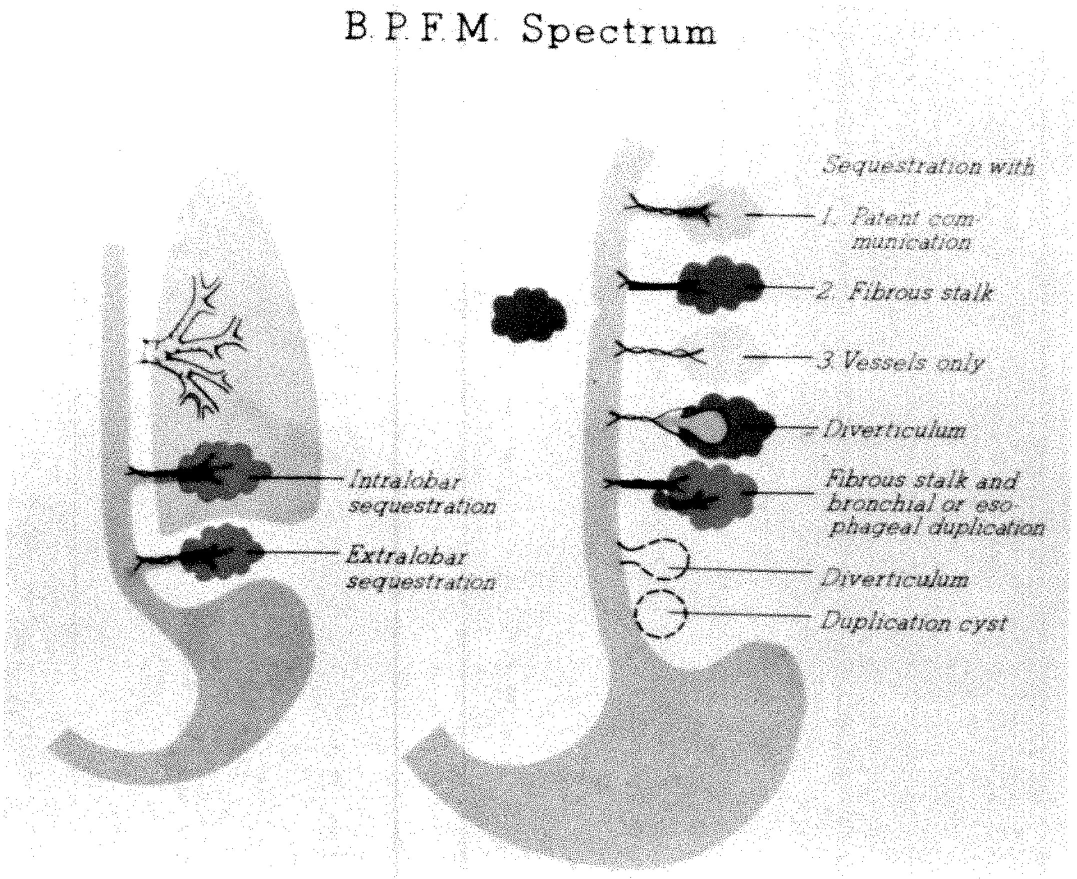

Fig. 9. Diagrammatic representation of the spectrum of bronchopulmonary foregut malformations.

The lumen of the duplication cyst communicated with the bronchus of the BPFM. This we feel represents the missing link in the evidence necessary for acceptance of the theory of common embryogenesis of the spectrum of bronchopulmonary foregut malformations described diagrammatically in Figure 9. The frank embryologic communication between two distinct congenital anomalies of the foregut indicates origin from a common precursor; their attachment to the esophagus by the fibrous stalk indicated that the precursor arose from the gastrointestinal tract.

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We are indebted to Dr. E. A. Boyden for reviewing the manuscript and the prints, and offering constructive criticism. He concurred with the Unifying Concept of Bronchopulmonary Foregut Malformations presented here but emphasized the fact that "the development of the bronchopulmonary segments and the associated anomalies is so complex that rarely can one hypothesis cover all variations."

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NEUROEPITHELIAL (COLLOID) CYSTS*

PATHOGENESIS AND UNUSUAL FEATURES

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ABSTRACT:

A brief history of the theories of pathogenesis of the origin of neuroepithelial cysts is presented. An origin more diffuse than the paraphysis seems most likely in our opinion, and we attempt to substantiate this theory with several of the cases from our series. One posterior third ventricular neuroepithelial cyst and one in the fourth ventricle are demonstrated roentgenographically. Also included in our series are a case showing suprasellar calcification on plain skull roentgenograms, not previously reported in neuroepithelial cysts, and a case with a cyst measuring 9 cm, the largest neuroepithelial cyst yet reported.

IN 1909, Sjovall[11] proposed that "colloid" cysts are derived from the embryonic structure, the paraphysis. Consequently, the term "paraphyseal cyst" gained common acceptance and wide usage over the next half century. However, two new theories of pathogenesis of these cysts have emerged over the past two decades in the neurological literature. Neither theory focuses primarily on the paraphysis, but rather on the neuroepithelium lining the primitive ventricular system, as the structure giving rise to the cysts. The purposes of this paper are to introduce these recent ideas concerning the source, development, and location of neuroepithelial cysts to the radiological literature, and to present our series of nine cases in tabular form, which we feel support the theories that neuroepithelial cysts do not necessarily arise from the paraphysis.

DISCUSSION

The paraphysis is a structure of unknown function which, according to Kappers[3] exists transiently in the human embryo as it develops from a crown-rump length of 17 mm to 100 mm (approximately 7–14 weeks). Normally the paraphysis has completely regressed by the 145 mm stage. The principal structure develops in the midline of the diencephalic roof just rostral to the telencephalic border (Fig. 1) but smaller *Anlagen* may occur lateral to the midline. Microscopically the low columnar paraphyseal epithelium is distinguished from surrounding epithelium by the absence of cilia and blepharoplasts.

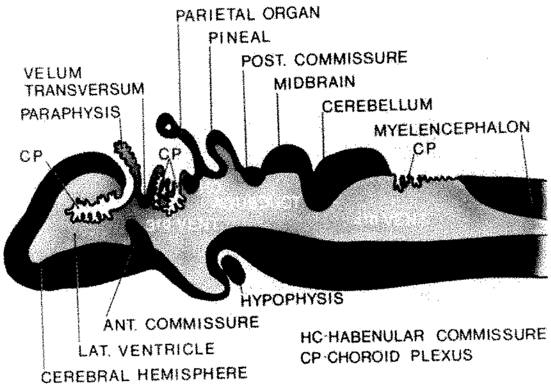

FIG. 1. Diagram of the primitive embryonic brain with demonstration of the developing paraphysis and the choroid plexus.

The neuroepithelial cysts reported in the third and fourth ventricles have demonstrated marked epithelial proliferation and variation of cell types and organelles: goblet cells, vacuolated cells, blepharoplasts, and cilia. Tubule formation in the wall of the cysts is common.[10]

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Kappers[3] proposed that, while occasionally cysts may develop from either the central or peripheral paraphyseal *Anlagen* in the roof of the third ventricle, more frequently cysts arise from potentially larger diencephalic roof ependymal recesses. These can pinch off into closed vesicles in the course of brain development. These cysts of ependymal origin have similar low columnar epithelium, and may include goblet cells, but, unlike the paraphysis, cilia and blepharoplasts are also present. This theory allows for wider distribution and size variation in third ventricle cysts than does Sjovall's[11] assertion of a paraphyseal origin of colloid cysts. The differentiation of paraphyseal from diencephalic roof cysts is made by the type of epithelial lining. In either type of cyst, the gelatinous colloid within appears to be secreted by the epithelial lining.

An alternative theory of the pathogenesis of neuroepithelial cysts was proposed by Shuangshoti *et al.*[9] and expanded by Shuangshoti and Netsky.[10] The theory can be substantiated by a review of the developmental and comparative anatomy. Embryologically, the diencephalic roof plate consists of a non-nervous vascular mesenchyme, the tela choroidea, lined by a single layer of ependyma, the neuroepithelium. The mesenchyme and neuroepithelium form a transverse fold, the velum transversum, separating the ventricles of the primary and secondary forebrain. The neuroepithelial roof of the diencephalon becomes thin on either side of the velum transversum. The vascular mesenchyme on the dorsal surface of the roof pushes the neuroepithelium into finger-like processes in the third ventricle, becoming the anterior choroid plexus (plexus of the third ventricle). The epithelial covering is therefore continuous at the roof of the plexus with the ependymal lining of the third ventricle.

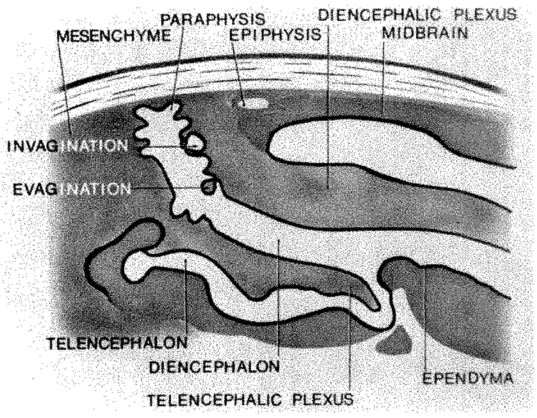

Fig. 2. Diagrammatic model depicting invagination and evagination of neuroepithelium in the roof of the third ventricle, a process which can explain why epithelium or connective tissue can line a neuroepithelial cyst.

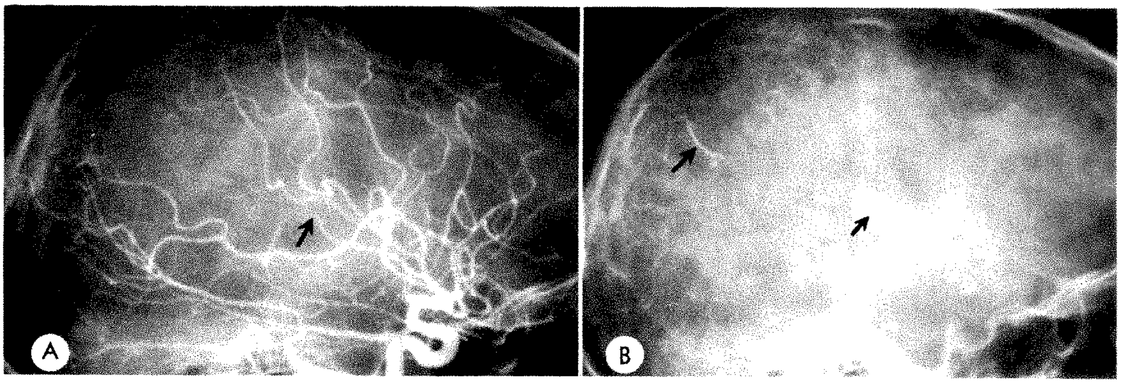

Fig. 3. Carotid arteriograms in Case II demonstrate (*A*) obstruction of a posterior parietal branch of the middle cerebral artery (arrow) due to sudden onset of increased intracranial pressure. (*B*) Note delayed retrograde filling of the obstructed branch (arrows).

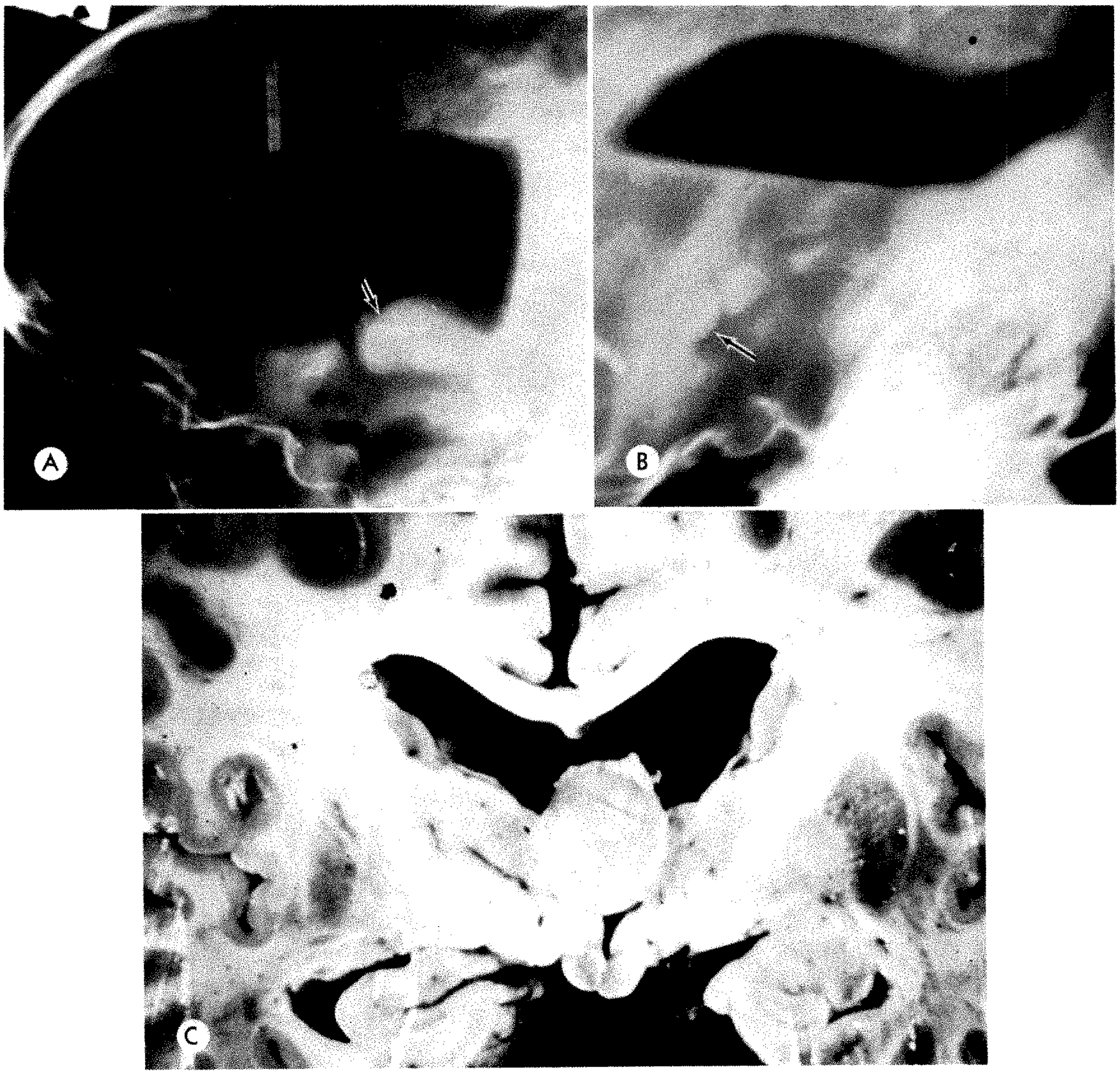

FIG. 4. (*A* and *B*) Pneumograms and (*C*) pathological specimen of Case II demonstrating an anterior third ventricle mass (arrows).

On the dorsal surface of the diencephalic roof, just anterior to the velum transversum, the neuroepithelium evaginates to form the paraphysis in nearly all vertebrates, including man. The organ reaches its highest development in amphibians and reptiles, particularly Urodeles, and is rudimentary in mammals.

There is, therefore, clearcut evidence that the original choroid plexus and the paraphysis are derivatives of the neuroepithelial lining of the diencephalic roof. It has been clearly demonstrated by a number of authors in lower vertebrates and human embryos, that the paraphysis actually represents an extraventricular choroid plexus.[5,7,13]

McLean[6] and Van Wagenen[12] separated neuroepithelial cysts of the third ventricle from the common cysts of the choroid plexus on the basis of the histological lining of the cyst: choroid plexus cysts were lined by connective tissue, but neuroepithelial cysts were lined by epithelium. Shuangshoti *et al.*,[9] however, proposed that cysts can develop in any part of the ventricular system lined by the neuroepithelial layer from either invagination or evagination, with a connective tissue layer either outside or inside the neuroepithelial layer, respectively (Fig. 2). The position of the connective tissue in the cyst is therefore not a fundamental point in distinction of pathogenesis. Cystic lesions found in the pineal gland and choroid plexus in routine autopsies may be similar in the mechanism of formation to those in the third ventricle. These cysts were once thought to be due to regressive changes with age, but have been found with enough frequency in children to make the congenital basis of formation even more attractive.[10]

Shuangshoti *et al.*[9] furthermore assert that the histological presence or absence of various cellular organelles or cell types is merely an expression of normal variation of the regional neuroepithelium. In particular, cilia are explained to be present in all primitive neuroepithelium, but to disappear from many cells with time. Therefore, they discount the importance of the cellular differences which Kappers[3] considered diagnostic in histological examination of neuroepithelial cysts.

CLINICAL MATERIAL

Our present series of nine cases includes five males and four females, ranging in age from 22 to 45 years at initial presentation (Table 1). This is consistent with most other reported series of neuroepithelial cysts, with no significant sex predominance and initial symptoms occurring in the third through fifth decades. It was once felt that there was a classic history of presentation, characterized either by severe headaches of sudden onset induced by rapid change of position of the head; or by a picture of gradually degenerating mental capacity. Presumably, the former presentation would likely be produced by a pediculated, midline third ventricle tumor capable of obstructing the foramina of Monro or the aqueduct of Sylvius upon change of head

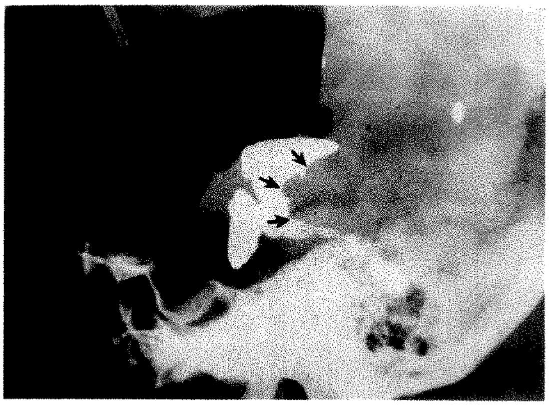

Fig. 5. Double contrast ventriculogram of Case iv demonstrating large posterior third ventricle mass (arrows).

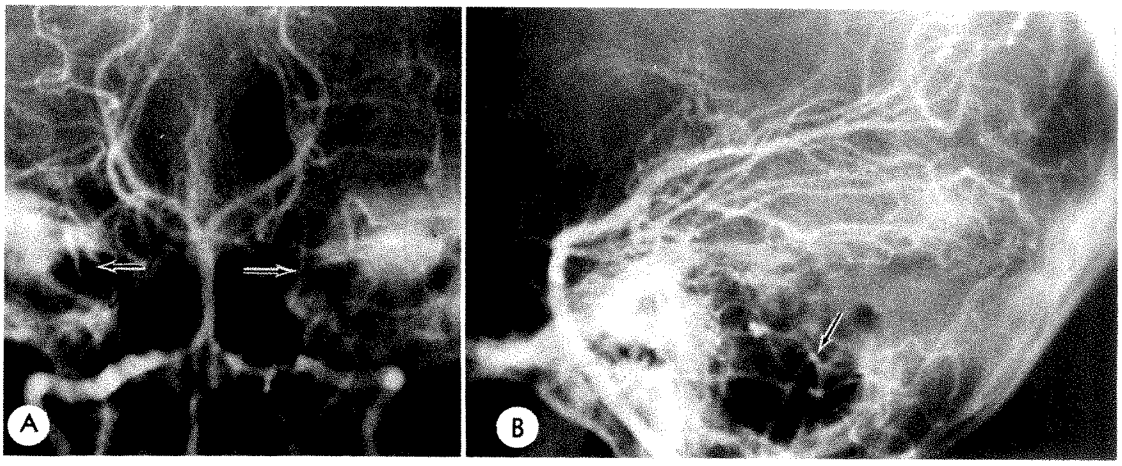

Fig. 6. (*A* and *B*) Vertebral arteriograms of Case ix showing lateral and downward displacement of the posterior inferior cerebellar arteries bilaterally (arrows) and note also, separation of their vermian branches.

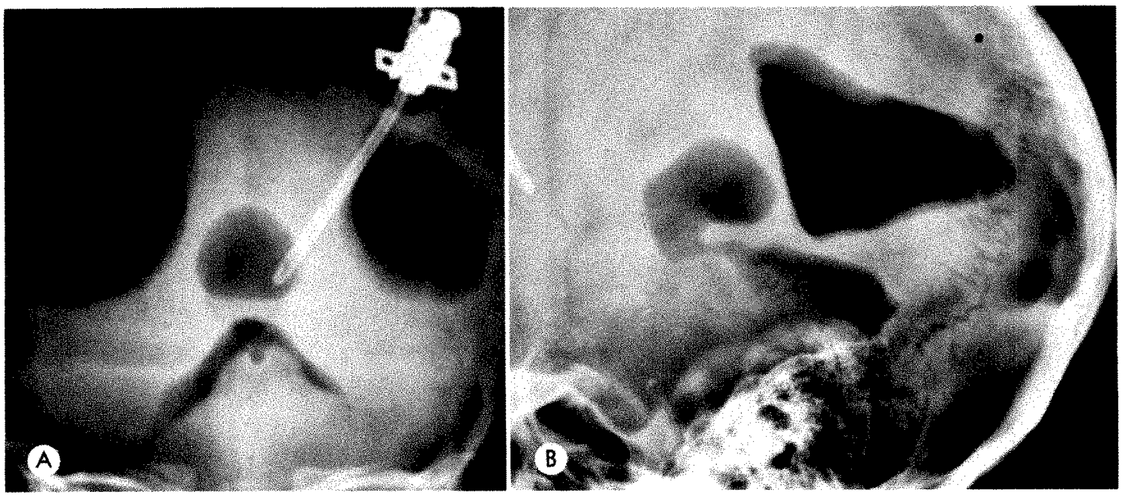

Fig. 7. (*A* and *B*) Ventriculograms of Case IX showing a large mass in the floor of the fourth ventricle.

position, producing a sudden onset of increased intracranial pressure. The latter history would be more consistent with a more sessile tumor mass causing gradually increasing intracranial pressure, with consequent progressive obstructive hydrocephalus.

As has been noted on more recent series, however, such classical histories are seldom related.[4] Our cases included such presentations as left-sided hemiparesis due to a vascular occlusive process, probably due to sudden increased intracranial pressure (Fig. 3, *A* and *B*; and 4, *A–C*) in Case II from Table I.

Included also in our series is a neuroepithelial cyst in the posterior part of the third ventricle (Case IV). As stated above, neuroepithelial cysts may arise wherever neuroepithelium is found in the central nervous system. Only one documented case of a posterior third ventricle neuroepithelial cyst has been reported however,[2] possibly due to misdiagnosis in the prevailing belief that these cysts could be found only anteriorly in the third ventricle, and the consequent assignment of another diagnosis, perhaps degenerative cysts, to those that have been found posteriorly in the third ventricle. The patient's double contrast ventriculogram is presented (Fig. 5). A microscopic view of the wall of the cyst showed it to be

Table I

	Age	Sex	Location	Size
1	28	F	3rd V.	1 cm
2	22	M	3rd V.	2 cm
3	44	M	3rd V.	2 cm
4	36	F	3rd V.	2.5 cm
5	45	M	3rd V.	3 cm
6	25	F	3rd V.	3.5 cm
7	39	F	3rd V.	4 cm
8	35	M	3rd V.	9 cm
9	25	M	4th V.	2.5 cm

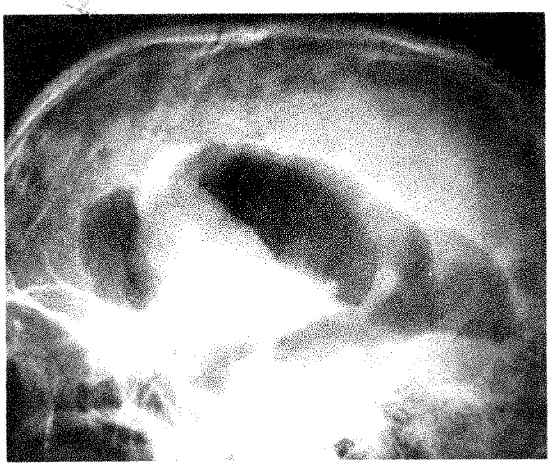

Fig. 8. Neuroepithelial cyst which measured nine cm in its largest diameter when excised. It extends almost to the level of the roof of the lateral ventricles.

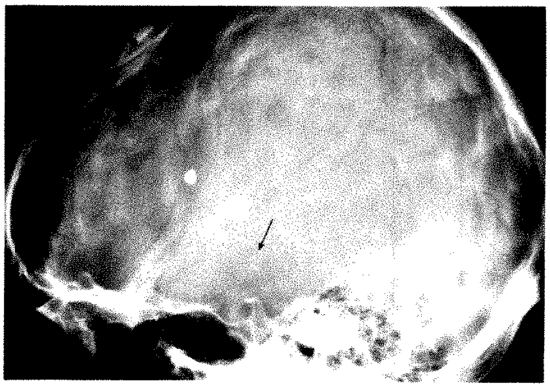

Fig. 9. Suprasellar calcification seen on plain skull roentgenogram of Case vii, which proved to be in the wall of the cyst (arrow). Note marked posterior displacement of the pineal gland.

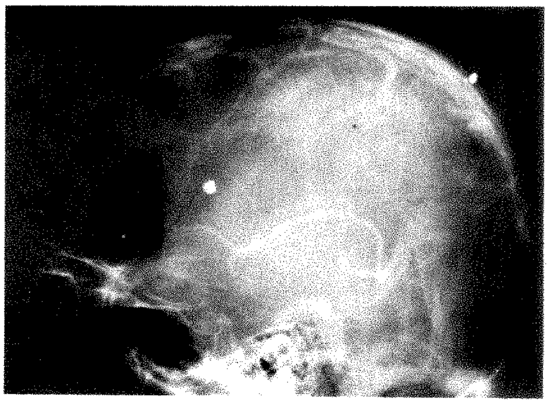

Fig. 10. Downward displacement of the anterior portion of the internal cerebral veins in Case vii due to encasement by tumor.

identical to neuroepithelial cysts of the anterior part of the third ventricle.

Another of our cases (Case ix) represented a neuroepithelial cyst of the fourth ventricle, the fifth so far reported in the literature.[8,10] The patient's vertebral arteriogram demonstrates a lateral and posterior displacement of the posterior inferior cerebellar arteries, with separation of their vermian branches (Fig. 6, *A* and *B*). The venous phase showed posterior displacement of the precentral cerebellar vein. The ventriculogram clearly outlines the tumor mass extending into the fourth ventricle from the floor of the ventricle (Fig. 7, *A* and *B*). The tumor proved to be peduncular on excision, and on microscopic section it was identical to, and in fact was, a neuroepithelial cyst.

Another of our cases was a 35 year old male (Case viii), presenting with headaches, ataxia, progressive dementia, and papilledema, who, at surgery, was found to have an anterior third ventricle tumor measuring 9 cm in its longest diameter, the largest neuroepithelial cyst so far reported to our knowledge (Fig. 8).

Finally, our Case vii proved unusual in

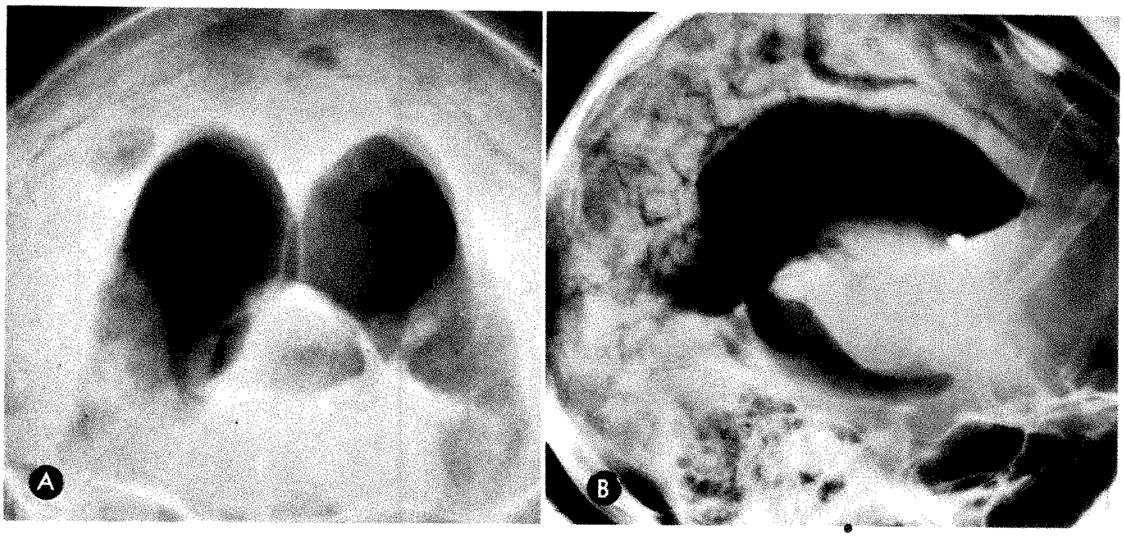

Fig. 11. (*A* and *B*) Pneumoventriculograms of Case vii show a large mass, obstructive hydrocephalus, and posterior and downward displacement of the posterior portion of the third ventricle.

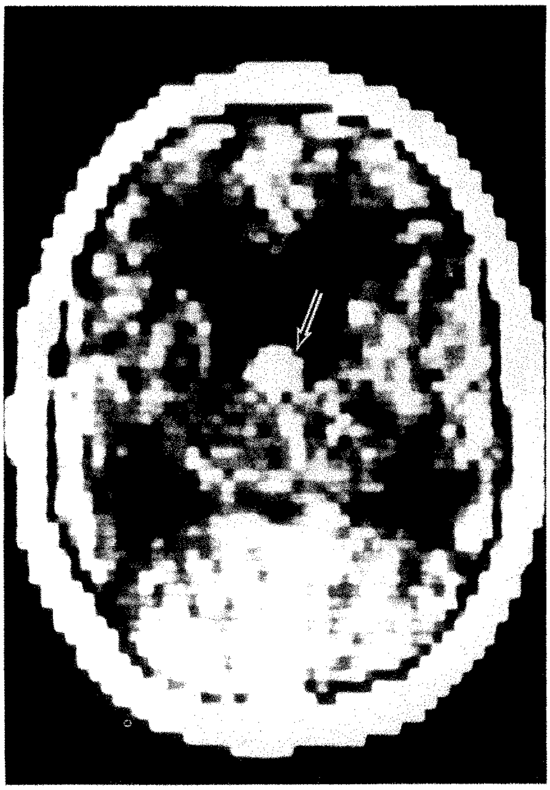

FIG. 12. Computerized tomogram demonstrating a dense mass (neuroepithelial cyst) in the area of the foramina of Monro (arrow), producing obstructive hydrocephalus.

that there was roentgenographically visible calcification on the skull roentgenogram (Fig. 9). Calcifications have been frequently found on microscopic sections of the walls of neuroepithelial cysts, but have not been reported on plain skull roentgenograms. The venous phase of the arteriogram demonstrates downward displacement of the internal cerebral veins, due to encasement by the tumor (Fig. 10). The pneumoventriculogram shows a large suprasellar mass (Fig. 11, *A* and *B*).

The recent use of computerized tomography has aided in the diagnosis of neuroepithelial cysts, as shown in an additional case (Fig. 12).

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Vol. 126, No. 1

OPTIMAL TOMOGRAPHIC TECHNIQUE TO DEMONSTRATE COMMON BILE DUCT STONES*

AN *IN VITRO* STUDY

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ABSTRACT:

Six degree and 10 degree circular modes represent the optimal methods available for intravenous cholangiography with tomography within the technical limitations and constraints outlined in this study. The 10 degree mode is superior in the presence of superimposed gas. Ten degree linear tomography is an efficient method for determining the level of the common bile duct but is not the optimal method for obtaining image detail.

Thin section unidirectional or pleuridirectional modes are occasionally helpful in delineating fine details. The zone of focus is very narrow, permitting very limited sampling within the usual zone of interest. These modes are inefficient in determining the level of the duct and produce less useful image detail than 10 degree circular tomography for ducts of normal, or slightly larger than normal diameters. They are seldom indicated as the primary modality in tomography of the common bile duct.

ALTHOUGH the use of tomography is well established for intravenous cholangiography (IVC), the optimal technique remains in question.[6,8,13] We prefer the term tomography or body section roentgenography to "laminagraphy" or "zonography" in this discussion.[3,12] Controversy surrounds both the choice of modes, unidirectional *versus* pleuridirectional, and the optimal filming arc.

Foy[7] advocated circular rather than linear tomography in intravenous cholangiograms. Love *et al.*[11,14] have tried circular tomography in gallbladder wall imaging but have discarded it in favor of very thin section (40 degree arc) linear tomography. Littleton and Winter[9,10] have used a hypocycloidal mode with success and have written extensively on the visual content of various tomographic modalities. They, among others,[2] have consistently advocated tomography for optimal visualization of the common bile duct.

While an optimal image of the opacified bile duct is the obvious goal for roentgenography, several other issues are of concern in the choice of tomographic technique. The first of these is the inability of some patients to suspend respiration for periods necessary to complete an exposure with certain thin section methods. Flexibility in tomographic filming techniques is required to accommodate oversized, severely ill, or poorly cooperating patients. A second problem is the localization of the plane of interest; that is, the determination of the anatomic level of the biliary tract. It is desirable that this be done with the minimum of time, film, and patient exposure. Because we were unsatisfied that these and other problems had been resolved definitively, it seemed worthwhile to re-evaluate cholangiography as produced by each of the tomographic techniques currently available.

METHOD

Drawbacks encountered by other workers[7,20] who have attempted to carry out studies of intravenous cholangiography

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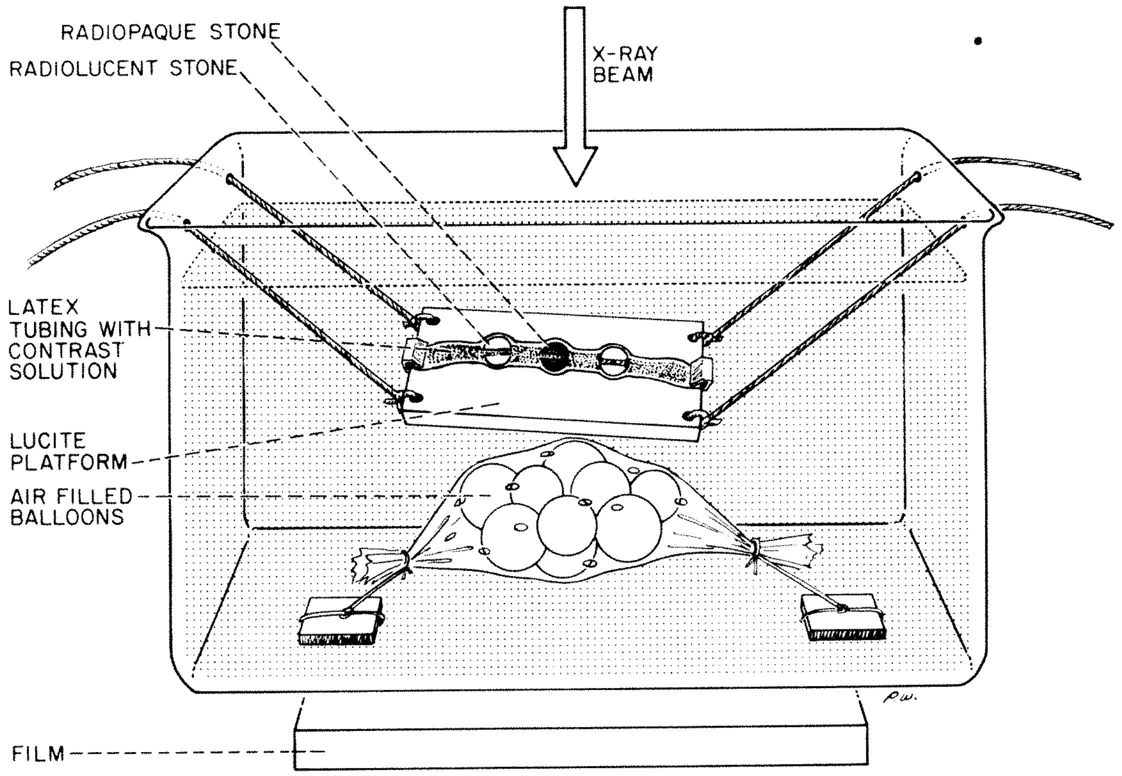

FIG. 1. Line drawing of the common bile duct phantom indicating the simulated common bile duct at an angle to simulate the morphological relationship of the normal common bile duct with the body. The line drawing is not intended to be entirely in scale.

with human subjects can be overcome by employing appropriate phantoms. The validity of such test objects has been well established in the roentgenologic literature.[4,5,15,16,17,19] We decided to construct a phantom that would allow a selection of several qualities at will. These qualities were:

1. Dimensions and orientation of the "common bile duct."
2. Iodide concentration of its contents.
3. Size, shape, number, position, and radiolucency of artificial "common duct stones."
4. Thickness of the "subject."
5. Interposition of "bowel gas."

For the experiments to be described below, a synthetic common bile duct with an internal diameter of 5 mm was constructed from flexible radiolucent latex rubber tubing. Two spherical radiolucent beads and one radiopaque bead, all having external diameters of 7 mm were introduced into the lumen of the tube to simulate stones, with the opaque stone in the center and the lucent stones 2.5 cm on either side. The 2 mm difference in the diameter of the tube and stones insured that the stones would remain in a fixed position. A single hole through each bead permitted free flow of iodide solution throughout the tube (Fig. 1).

The opacified bile was mimicked by diluting 20 ml of Meglumine Iodipamide (Cholografin-Squibb) with 500 ml of five percent dextrose in water. The tube was filled with the contrast agent and positioned on an adjustable platform and immersed in a water bath 18 cm deep, to a level 5.5 cm beneath the surface. The bath and platform additionally interposed 7 mm of lucite and 5 mm of polyethylene between the tubing and the film.

In one set of experiments the tubing was placed horizontal. In a second set it was inclined 30 degrees with respect to the horizontal plane and 35 degrees from the axis of linear tomography in an attempt to reproduce the morphological orientation of the common bile duct in human subjects. Bowel gas was simulated in the phantom by anchoring nine air-filled rubber balloons transversely immediately beneath the tubing. These balloons measured approximately 4 cm×3 cm×3 cm. While the selection noted above was arbitrary, values chosen were judged to represent a reasonable replication of a typical patient for intravenous cholangiography.

ROENTGEN STUDIES

We used a Philips-Massion Horizontal Polytome. Technical factors and equipment included were a Philips Super-70 generator with a Philips Rotalix tube having a nominal 1.2 mm focal spot size and a filtration factor of 1 mm of aluminum; a single Philips Cassette XH-2001/25 (10″×12″), with Radelin TF-2 High Speed Screen, and Par Screen G.A.F. Corporation film; and a 10:1 rotating grid. A 90 second Kodak X-Omat processor was used with G.A.F. film chemistry.

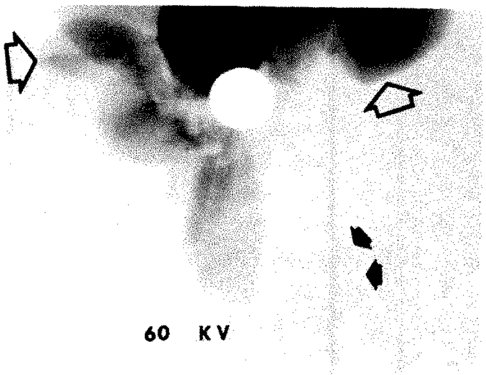

Fig. 2. Phototimed film of the phantom, without tomography, at 60 kv. Note the dense radiopaque bead and the lucency of the nonradiopaque bead (solid arrows) contrasting with the Cholografin solution in the latex tubing. The dense shadows overlying the center of the figure are the air-filled balloons. The second radiolucent stone is completely obscured by the underlying gas (open arrows) and could not be seen without tomography.

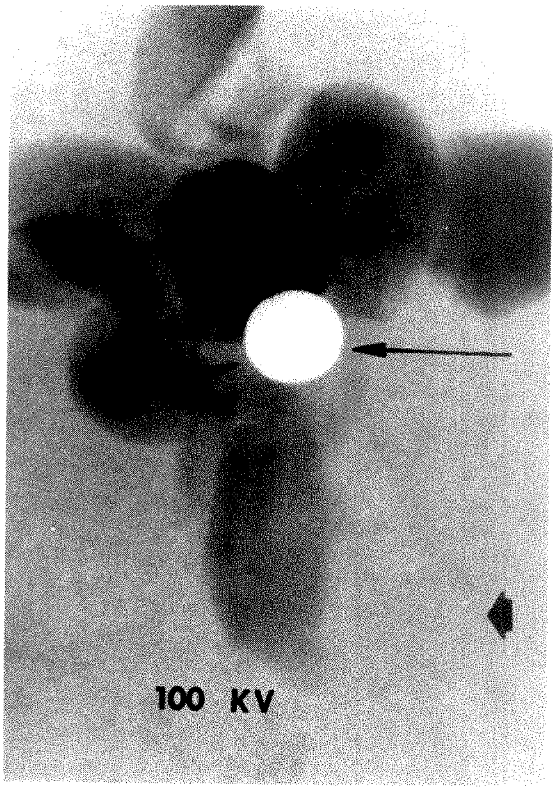

Fig. 3. This film is the same projection as Figure 2 except that the kilovoltage has been increased to 100 kv. The increased kilovoltage has dramatically reduced the contrast between the lucent bead (solid arrow) and the Cholografin solution. The radiopaque stone (line arrows) is not altered from its image from the 60 kv film.

The Philips Polytome was capable of unidirectional or pleuridirectional movement with blurring angle adjustable from six to 60 degrees. Depending on the mode selected, the exposure times varied between the extremes of 0.15 seconds and 6.0 seconds.

In common bile duct imaging it is desirable to keep the tube voltage as close to 68 kv as possible to produce maximum roentgen-ray beam absorption by iodine (Fig. 2; and 3). To approach this objective, the highest mas permitted by tube rating was generally used. Our options were 10, 15, 25, 50, 75, and 150 ma.* The lowest peak kilovoltage was chosen which produced a satisfactory darkening of the most

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* Operator's Manual, Philips Polytome U. XD 4094-SPX-68.2.

Table I

SUMMARY OF RADIOLOGISTS' EVALUATIONS OF THE ROENTGENOGRAMS OF THE PHANTOM COMMON BILE DUCT

	Tomographic Zone of Focus	Exposure Time	Mean Ranking of Phantom Image* Detail	
			With Overlying Gas	No Overlying Gas
10 Degree Linear	6.9 mm	0.15 sec	3.8	4.8
40 Degree Linear	1.65 mm	0.62 sec	3.0	4.7
6 Degree Circular	11.4 mm	3.0 sec	4.8	1.0
10 Degree Circular	6.9 mm	3.0 sec	1.3	1.8
20 Degree Circular	3.4 mm	3.0 sec	4.7	4.2
36 Degree Circular	1.8 mm	3.0 sec	6.3	7.1
40 Degree Ellipsoidal	1.65 mm	3.0 sec	5.1	4.8
48 Degree Hypocycloidal	1.35 mm	6.0 sec	7.0	7.5

* In a ranking scale from 1 to 8: 1=optimal image detail; 8=least image detail.
Philips Polytome U. Operators Manual XD 4004 SPX-68.2.

lucent part of the object. In determining the technique for each mode we set the mas high, the time being a fixed parameter, and adjusted our kv to obtain sufficient darkening. A high kv was necessary for the linear ten degree arc modality due to the short fixed exposure time. The other modalities had exposure times that allowed us to keep the kv relatively close to 68 kv. We are aware that other equipment could offer more flexibility.

The phantom was exposed with a beam collimated to $4\frac{1}{2}'' \times 5\frac{1}{2}''$ in the following modes: ten degree and 40 degree linear; six degree, ten degree, 20 degree, 36 degree circular; 40 degree transverse ellipsoidal; and 48 degree hypocycloidal.

RESULTS

A panel of four faculty radiologists and three radiology residents with more than two years of specialty training was assembled to review the roentgenographic results. The presentation of roentgenograms took place on an individual basis with eight randomly arranged images presented simultaneously for preference ranking. The panelists were permitted to move the films for side-by-side comparison and to employ conventional visual aids. All identifying marks on the films were masked. Each of the four faculty panelists reviewed the same set of images on a second occasion more than one week after this first encounter with them, so that the degree of his internal consistency could be established. The results of this evaluation are presented in tabular form (Table 1). The following pertinent observations were made.

Ten Degree Linear Tomography. (Technical Factors: 86 kv, 150 ma, 0.15 seconds.) Ten degree linear tomography was noted to produce an image of the duct even when the image plane was 2 or 3 cm away from the true level of the duct. This latitude was advantageous in determining the level of the duct from widely separated tomographic cuts. If the precise level of the phantom stone happened to be selected, fair detail was obtained.

A disquieting aspect of the ten degree tomography was the suppression of the image of radiolucent "stones" by superimposition of dense linear ghosts of the opacified duct in off-level cuts. In this case the duct seemed to be in the plane of focus while it was actually many millimeters away (Fig. 4). There is little doubt that this artifact could occur in patients, masking radiolucent stones that perhaps could be found by using different tomographic modalities more sensitive to the true level of the duct system (Fig. 5). Thus, an avoidable error in diagnosis sensitivity would be introduced if one depended entirely on ten degree linear tomography.

A minor increase in detail could be obtained by making linear tomograms at right angles to the axis of the duct. The advantages of this technique were some increased sharpness of the duct image and diminished "ghosting."

Forty Degree Linear Tomography. (Technical Factors: 75 kv, 50 ma, 0.62 seconds.) Forty degree linear tomography produced more blurring of the duct when it was 2 or 3 cm away from the level of the plane than ten degree tomography. The area of interest could be significantly unsharp even if the phantom duct level were only 1 cm away from the tomographic plane. The level of the tomographic plane had to be very close to the true level of the opacified duct for satisfactory visualization.

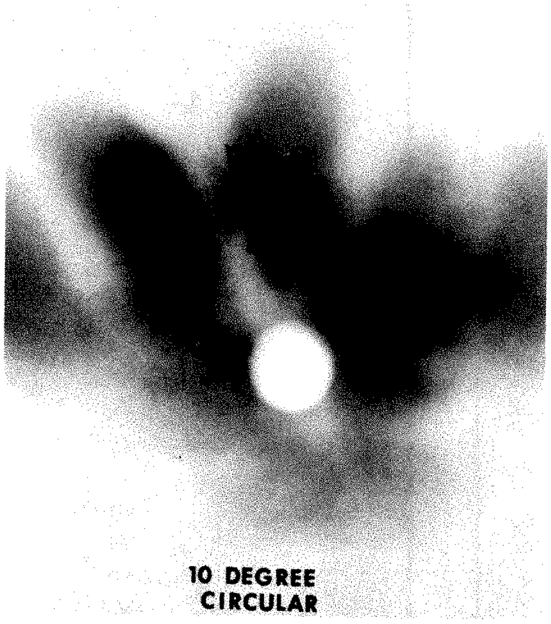

Fig. 4. Ten degree circular tomography at the true level of the radiolucent stone in the area of the underlying gas shadows. The lucent bead (open arrows) is separated from the underlying gas. The lower part of the tubing has been blurred away by tomography because it was 3 cm away from the zone of focus.

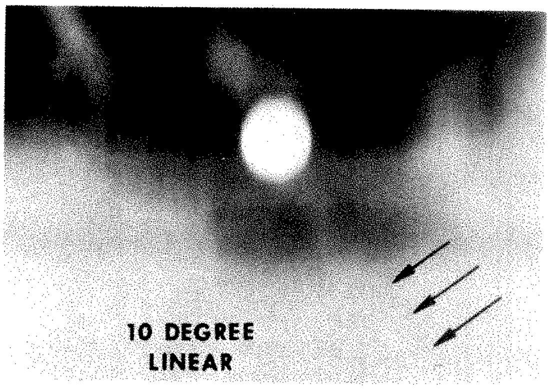

Fig. 5. Ten degree linear tomography at the true level of the radiolucent stone in the area of the overlying gas. The lucent stone is not readily visualized. However, the lower segment of the tubing shows as the "ghost" of the tube even though the zone of focus is 3 cm from that level (line arrows).

Additionally, a small change of kilovoltage seemed to make greater changes in the tomographic image in 40 degree tomography than the 10 degree tomography. This change correlated well with the longer exposure time, and the thicker average tissue layer exposed through a longer filming arc.

Once the precise level of the phantom stones was found the image was judged to be slightly better in this mode than the image in 10 degree linear tomography. However, the fact that the off-level common bile duct image was quite blurred and hazy tended to negate this slight advantage. The thin (1.65 mm) focus of the 40 degree arc did not optimally image the much thicker (5–7 mm) area of interest in the phantom.

Ten Degree Circular Tomography. (Technical Factors: 70 kv, 15 ma, 3.0 seconds.) Ten degree circular tomography produced very little ghosting of the phantom duct even when the tomographic zone of focus was very close to the true level of the duct. Occasionally it was difficult to localize the precise level of the duct with widely separated tomographic cuts. The detail of the phantom stone and duct was clearly superior to all other modes of tomography tested except 6 degree circular tomography. Especially attractive was the ability of circular tomography to eliminate confusing shadows of superimposed simulated bowel gas. Others have made these same observations in human subjects.[7,20]

Ten degree circular tomography was judged superior to 6 degree circular tomography in permitting the observer to recognize a stone when gas overlay the area examined. Ten degree circular tomography was also judged superior to 10 degree linear tomography in producing a sharp image.

Six Degree Circular Tomography. (Technical Factors: 70 kv, 15 ma, 3.0 seconds.) Although the zone of focus, 11.4 mm for this modality, is rather thick, the image details were surprisingly clear. This phenomenon has been well documented.[5] With respect to examination of simulated stones without overlying gas, this modality was judged superior to all other techniques. It was observed that an unsharp image of the duct was visible even when the tomographic level was several cm above or below the true level of the duct.

Twenty Degree Circular Tomography. (Technical Factors: 70 kv, 15 ma, 3.0 seconds.) This modality was judged to produce less usable image information than 10 degree circular tomography but to yield detail comparable to 10 degree and 40 degree linear tomography.

Thirty-six Degree Circular Tomography. (Technical Factors: 70 kv, 15 ma, 3.0 seconds.) This modality was judged inferior to both the 20 degree circular tomography and the 10 degree linear tomography in image quality and detail.

Forty Degree Transverse Ellipsoidal. (Technical Factors: 70 kv, 15 ma, 3.0 seconds.) This was inferior to the other modalities having a somewhat greater zone of focus. Aligning the axis of the ellipse at right angles to the course of the common bile duct was of little aid in improving the image.

Forty-eight Degree Hypocycloidal. (Technical Factors: 60 kv, 10 ma, 6 seconds.) This was judged inferior to the other modalities for IVC tomography. The useable information produced was minimal even at the level of the duct. The exposure time (six seconds) has clinical disadvantages.

DISCUSSION

The roentgenographic establishment of the exact level of the faintly visualized common bile duct is often difficult in human subjects. Normal respiratory movement, coughing, involuntary movement, or lack of the patient's full cooperation can alter the level of the common bile duct from film to film. This alteration becomes especially significant when thin section tomography is employed.

Meticulous technique in preliminary tomographic scout films is important. The ideal scout film has many shades of gray and includes both light and dark areas. Beam collimation and beam coning, including the use of extension cones, are recommended.[13,18] Special beam filters show promise in accentuating iodine absorption although we have no experience with these recent technical advances.[1]

A tomographic image is the endpoint of a complex process in which the interaction between object and filming system has a central location. Where the object of interest is non-homogeneous and has variable dimensions, identification of the contribution of any single element in the system to the final image becomes very difficult. We do not propose, therefore, that our results are necessarily those which would be obtained with a different object or different filming system. It is equally possible that an entirely different motion mode would produce superior images.[3,5,20]

One generalization does appear to be supported by our experiments. Optimal visualization of the duct was produced by a tomographic mode in which the zone of

Table II*[21]

14.0 mm	Upper range of a normal CBD
11.4 mm	6 degree arc tomogram plane of focus
6.9 mm	10 degree arc tomogram plane of focus
6.0 mm	Average diameter of CBD
3.45 mm	20 degree arc tomogram plane of focus
3.0 mm	Lower range of normal CBD diameter
1.84 mm	36 degree arc tomogram zone of focus
1.35 mm	48 degree arc tomogram zone of focus

* Philips Polytome U. Operators Manual XD 4004 SPX-68.2

focus closely matched the diameter of the examined structure[21] (Table II).

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SUCCESSFUL INTRAVENOUS CHOLECYSTOCHOLANGIOGRAPHY IN THE JAUNDICED PATIENT USING MEGLUMINE IODOXAMATE (CHOLOVUE)*

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ABSTRACT:

A clinical trial of meglumine iodoxamate (Cholovue) for intravenous cholangiocholecystography in 18 patients with elevated levels of serum bilirubin was performed. Ten to 30 cc of a 40 percent aqueous solution of the agent were given intravenously over a ten minute period and roentgenographic examinations conducted to document the agent's effectiveness, to determine optimal levels of dose, and to assess its safety.

Common bile duct and gallbladder visualization was obtained in a surprisingly large number. The agent was effective with bilirubin levels up to 6.5 mg percent. The optimal dose in patients with elevated bilirubin is probably in the range of 20 cc. Despite intensive monitoring, there were no important adverse clinical nor laboratory reactions observed.

The new agent appears to offer a significant improvement over Cholografin, particularly with respect to patients with elevated bilirubin levels.

MEGLUMINE iodoxamate (Cholovue) is a new intravenous cholangiocholecystographic agent, currently being evaluated in the United States under the auspices of the Squibb Institute for Medical Research.

Meglumine iodoxamate is not unlike meglumine iodipamide (Cholografin) in its molecular structure. The major difference is the composition of the linkage between the tri-iodinated benzoic acid radicals. Iodoxamic acid has a molecular weight of 1,287.9 and a molecular iodine content of 59.1 percent. The meglumine salt has a molecular weight of 1,678.3 and molecular iodine content of 45.5 percent. The molecular structure of iodoxamic acid is depicted in Figure 1.

In preclinical test evaluations performed in mice, rats, and dogs, meglumine iodoxamate was distinguished from iodipamide (Cholografin) and ioglycamide (Bilivistan) by lower acute toxicity and better biliary excretion.[3] It was, therefore, anticipated that the agent would be potentially better tolerated in human patients and would afford better visualization.

Clinical trials performed in Europe have helped to determine the tolerance of the contrast agent and ascertain the optimal time of exposure, as well as document effectiveness. The over-all impression of numerous investigators who studied the agent was that meglumine iodoxamate was well tolerated and produced a significantly high percentage of acceptable roentgenologic examinations. Adverse effects encountered were not unusual in type or number. Those noted were typical of those reported for any intravenous contrast agent, in numbers not unlike those for currently available media.[2]

Sargent *et al.*[4] conducted the first clinical study in the United States. Eighteen patients with essentially normal biliary function were studied. The agent was found to be rapidly excreted and proved highly effective for visualization of subhepatic, hepatic and common bile ducts as well as the gallbladder. No important adverse effects were reported. The optimal intravenous dose was thought to be approximately 20 cc of the 40 percent aqueous solution used.

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The purpose of the present study is threefold: first, to ascertain whether the agent is effective in the presence of jaundice; second, to determine the optimal dose of meglumine iodoxamate required to obtain satisfactory opacification of the bile ducts and gallbladder in patients with impaired hepatic function; and third, to determine any potential detrimental effects by the new agent on the liver and other organ systems in the presence of such hepatic impairment.

MATERIAL AND METHOD

The patients studied were men between the ages of 18 and 60, who had no evidence by either history or physical examination of active renal, hematopoietic or myocardial disease. Any patients with significant abnormalities on the electrocardiogram or with glucose-6-phosphate dehydrogenase deficiency were excluded. Patients with a history of asthma, allergy, or thyroid disease were excluded, as were those who had been treated with any contrast agent in the preceding seven days. The patients were restrained from ingesting caffeine or alcohol-containing beverages, and smoking during the 24 hours preceding the examination and throughout the remaining course of the study.

A complete battery of laboratory studies was performed prior to the study, as well as at 4, 8, 24, 48 and 120 hours after administration of the contrast agent. The laboratory evaluations included the following:

Hematology—hemoglobin, hematocrit, total leukocyte count, differential count, platelet count.

Urinalysis—pH, specific gravity, protein, sugar, microscopic evaluation of sediment.

Serum chemistry—urea nitrogen, serum glutamic oxalocetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), alkaline phosphatase, serum bilirubin (direct and total), uric acid, cholesterol, calcium, phosphorus, total protein, albumin, lactic dehydrogenase, creatinine, creatine phosphokinase, glucose, sodium, potassium, chloride, carbon dioxide.

IODOXAMIC ACID

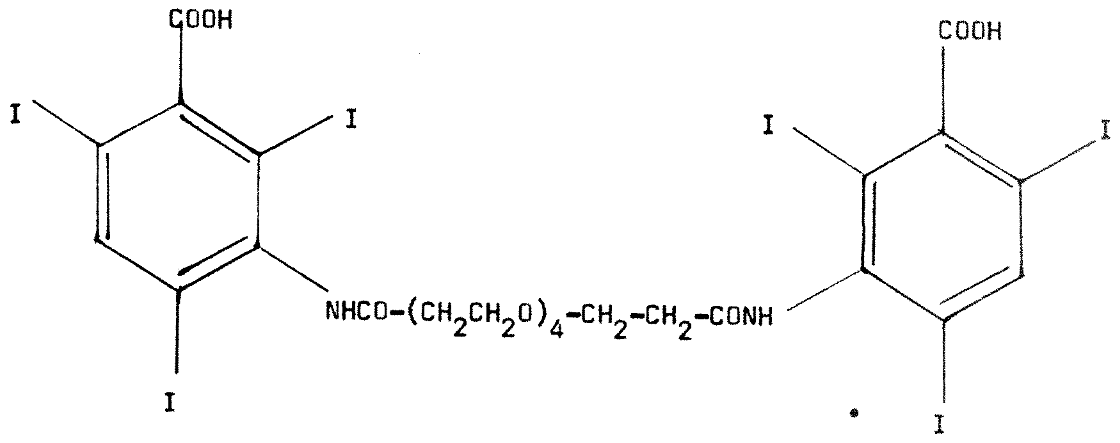

Fig. 1. Molecular structure of iodoxamic acid.

Table I

Group	Dose	Serum Bilirubin	
		2–4.9 mg percent	5–8 mg percent
I	10 ml	3 patients	3 patients
II	20 ml	3 patients	3 patients
III	30 ml	3 patients	3 patients

Creatinine clearance was determined prior to enrollment and 24 hours post-drug only.

Serum protein electrophoresis, 5 S′ nucleotidase and prothrombin time were obtained at enrollment and 120 hours post-drug only.

Red cell glucose-6-phosphate dehydrogenase and testing for hepatitis B surface antigen in serum were done only to screen out positives.

Physical examinations were performed immediately prior to administration of the drug, and repeated at 2, 24, and 120 hours post-drug administration. Vital signs were obtained additionally at the conclusion of injection, 30 minutes, one hour and four hours after administration of the contrast agent. A twelve lead electrocardiogram was performed prior to injection, as well as at 4, 24, and 120 hours after drug administration. Electrocardiogram monitoring was obtained continuously during the injection up to the time of the first roentgenogram.

The 18 patients were subdivided into groupings dependent upon the dose of contrast agent used, either 10, 20 or 30 ml of a 40 percent aqueous solution and by serum bilirubin lying within the 2 to 4.9 range, or the 5 to 8 mg percent range as outlined in Table I. As shown, six patients were assigned to each dose level. For each of the three dosages studied, three of the six patients had a level of total bilirubin of 2–4.9 mg percent and three patients had a level of 5–8 mg percent.

The patients were selected with the intent that each was to have a stable clinical and laboratory picture. The study was generally conducted in an ascending dose fashion; *i.e.*, 10 ml doses were studied first, then the 20 and 30 ml doses, respectively.

Essentially no bowel preparation was used, but the patients were kept on a low-residue diet prior to the study and were allowed to take nothing by mouth in the six hours prior to the examination except water.

The total volume of contrast agent was injected slowly over a ten minute interval in each case.

Roentgenography was performed with the patient recumbent, and the left side elevated at 15, 30, 45, 60, 90, 120, 150, 180 and 240 minute intervals after completion of the injection. If visualization was not obtained after four hours, roentgenograms were taken at 8 and 24 hour intervals as well. Laminagraphy was performed in all patients at a time deemed appropriate by the radiologist, usually during the interval between 40 and 90 minutes.

Opacification of the biliary tract on the roentgenograms was evaluated on a grade of 0 to 4, the ducts and gallbladder being evaluated separately. Zero equaled no opacification, one equaled poor, two fair, three good and four excellent opacification, respectively.

RESULTS

Table II summarizes the results obtained in the 18 patients studied. All patients were studied to rule out biliary duct obstruction. The final diagnoses included 13 patients with cirrhosis or alcoholic hepatitis, or both, two with viral hepatitis, one with isoniazid hepatitis, one with cholangitis, and one with choledochocholelithiasis. Duct obstruction was not found in any of the patients. While not a prerequisite for the study, it so happened that all patients studied had not undergone previous cholecystectomy.

Over-all, 12 of 18 duct systems were visualized and 14 of 18 gallbladders were seen. Whether the one patient whose common bile duct was seen and gallbladder not visualized had gallbladder pathology has not yet been ascertained by surgical follow-up. The gallbladder was opacified in three patients whose ducts did not visualize. The degree of opacification was sufficiently great to allow visualization of intrahepatic ducts in four patients. Two representative cases are depicted in Figure 2 and 3.

In patients with bilirubin in the range of 2 to 4.9, there was little difference encountered between the 10, 20 and 30 cc doses. On the other hand, more patients in the bilirubin range of five to eight showed visualization when the higher dosages were employed.

Table III summarizes the relationship of visualization to serum bilirubin levels. Remarkable success was obtained in those patients with serum bilirubin between two and seven. There was no visualization in any patient with serum bilirubin greater than 6.5, although it is worth noting that only two patients in this study had serum bilirubin levels above 6.5 and fortuitously were ones that received only 10 cc of contrast material. Of those that visualized either duct system or gallbladder (15 of 18), twelve were confirmed by follow-up to have stable elevations of bilirubin, while three proved to have falling values over the five day follow-up. None was found to have a consistently rising serum bilirubin level over the five day follow-up, although several showed minimal elevations four to eight hours after injection.

There seemed to be no statistically definable correlation between success of the study and serum alkaline phosphatase or albumin levels, but one can easily note the general observation that poorer results were frequently obtained in patients whose alkaline phosphatase levels were in the higher ranges.

Of the twelve duct systems visualized, the average appearance time of the contrast agent in the ducts after completion of

Table II

SUMMARY OF DATA

Patient No.	Dose	Total Bilirubin	Alkaline Phosphatase	Albumin	Bile Ducts*	Gallbladder*
1	10 cc	4.9	197.4	3.2	2	4
2	10 cc	2.8	167.0	4.3	3	4
3	10 cc	2.4	92.8	2.8	1	1
4	10 cc	5.7	450.0	2.8	0	2
5	10 cc	7.6	199.6	1.5	0	0
6	10 cc	7.8	162.0	1.4	0	0
7	20 cc	3.8	220.0	2.2	3	3
8	20 cc	2.2	230.0	2.4	0	0
9	20 cc	3.1	150.9	2.9	1	1
10	20 cc	5.7	205.0	2.4	1	0
11	20 cc	6.5	122.3	4.1	0	1
12	20 cc	5.8	198.8	2.4	2	3
13	30 cc	4.7	114.0	1.8	2	1
14	30 cc	2.8	95.0	2.2	2	1
15	30 cc	2.0	550.0	2.6	2	4
16	30 cc	5.1	125.0	2.6	2	2
17	30 cc	5.5	475.0	3.4	0	2
18	30 cc	6.5	110.0	3.3	4	4

* Rating Scale of Degree of Opacification: 0 = None; 1 = Poor; 2 = Fair; 3 = Good; 4 = Excellent.
Normal Laboratory Values at this Hospital: Total Bilirubin 0.2–1.2; Alkaline Phosphatase 17.0–78.0; Albumin 4.2–5.3.

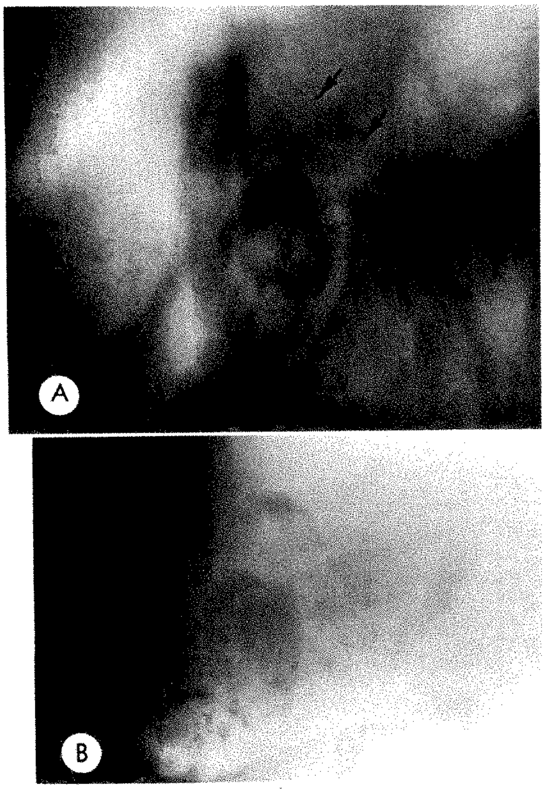

Fig. 2. (Pt. No. 7) A 47 year old chronic alcoholic. Total serum bilirubin at time of study 3.8, two days later 2.3 and five days after the study 2.2. (*A*) Laminagram at 55 minutes shows fair opacification of the common duct. (*B*) Upright roentgenogram at five hour interval confirms the presence of calculi within the gallbladder.

the injection was 41 minutes with extremes varying from 15 to 120 minutes. Maximum opacification occurred on the average at 59 minutes with extremes of 30 and 150 minutes. Of the 14 gallbladders visualized, the average time of initial visualization occurred at 87 minutes, varying from 30 to 240 minutes. Maximum opacification occurred on the average at 152 minutes, varying from 60 to 240 minutes.

Excretion of the contrast agent by the kidneys was readily visible in many examinations. Among those patients who received a 10 cc dose, none showed opacification of the urinary tract, while all of those who received 20 or 30 cc of contrast agent showed a pyelogram.

In the dosages used, meglumine iodoxamate was well tolerated without any important adverse reactions. Specifically, no evidence of any significant cardiovascular or electrocardiographic phenomena was found. No allergic reactions occurred. One patient showed a prolonged lymphocytosis after the study which was attributed to subsequently diagnosed hepatitis. Otherwise, no alterations of significance in the laboratory findings were noted. Minimal alterations were observed in several patients, but were felt to be consistent with normal laboratory variation.

DISCUSSION

Successful visualization of the gallbladder was obtained in 14 of the patients studied, and the common bile duct in twelve of these. The agent was effective in patients with total bilirubin levels as high as 6.5. While some of these individuals were subsequently shown to have falling values, thus enhancing the chance of visualization, the majority that visualized did not fall into this category. Significantly, none in

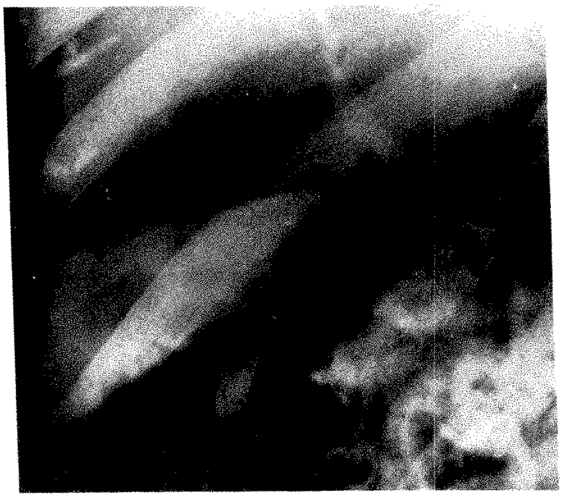

Fig. 3. (Pt. No. 18) A 51 year old alcoholic, acutely jaundiced. Total serum bilirubin at the time of the study was 6.5, two days later 4.6 and five days after the study 4.1. Sixty minute plain roentgenogram shows excellent opacification of subhepatic, hepatic and common bile ducts as well as the gallbladder.

Table III

RELATION OF SERUM BILIRUBIN TO VISUALIZATION

Total Bilirubin	Visualized Ducts	Percent	Visualized Gallbladder	Percent
2–3	4/5	80	4/5	80
3–4	2/2	100	2/2	100
4–5	2/2	100	2/2	100
5–6	3/5	60	4/5	80
6–7	1/2	50	2/2	100
7–8	0/2	0	0/2	0

the study group had a rising bilirubin because of the selection process required, nor did any of the patients have extrahepatic obstruction. While visualization may have been considered to be faint or poor, there was significant clinical information obtained in virtually all cases where any visualization was obtained.

The results are impressive when compared to the reported effectiveness of iodipamide. Only 30 to 40 percent success has been reported in the bilirubin ranges of two to four while very little in the way of visualization has been reported in the range greater than four.[5] Indeed, in the patient population that is routinely seen at our institution, the over-all success has been considerably worse than reported data. Our previous results in such patients have been so disappointing as to warrant not recommending intravenous cholangiography in any patient with a bilirubin of greater than two. For that reason iodoxamate seems to offer significant promise.

We have not found a striking early appearance of the contrast agent as did Sargent *et al.*[4] in studying patients with normal bilirubin levels. Our results are in agreement with recent experiments in animals that showed delayed excretion of contrast agent in the presence of hepatic dysfunction.[1] It would appear that the optimal time for common bile duct roentgenography usually lies between 45 and 60 minutes. For adequate visualization of the gallbladder in this patient group, we frequently had to follow the patients for as long as four hours. However, if not visualized by that interval, it became apparent that no further visualization would be obtained, *i.e.*, no additional information was obtained, on eight and 24 hour roentgenograms.

On the basis of this study, it seems that in patients with bilirubin levels between 5 and 8 mg percent, more optimal visualization was apt to be obtained using the 30 cc dose (5.5 gm percent of iodine). Perusal of the data on the patients with bilirubins of 2 to 4.9 mg percent does not indicate an apparent dose-visualization relationship. This appears to be somewhat contrary to the impression obtained by Sargent *et al.*[4] in their initial clinical trial. It is possible that the impaired function of the liver allows more easy saturation of this organ's excretion capabilities with more overflow into the urinary system. As noted earlier, a pyelogram was observable in all patients who received 20 cc or more. This may well reflect only variation due to the small size of the patient sample studied. This point will have to be clarified after more extensive clinical trials. For that purpose an extensive double-blind comparison of Cholovue *versus* Cholografin is currently underway which we believe may help resolve this and many additional questions.

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GRIFFITHS' POINT: CRITICAL ANASTOMOSIS AT THE SPLENIC FLEXURE*

SIGNIFICANCE IN ISCHEMIA OF THE COLON

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ABSTRACT:

Griffiths' point is defined as the site of (a) communication of the ascending left colic artery with the marginal artery of Drummond, and (b) anastomotic bridging between the right and left terminal branches of the ascending left colic artery at the splenic flexure of the colon. It is upon this critical point at the splenic flexure that collateral circulation between the superior mesenteric artery and the marginal artery branch of the inferior mesenteric artery supplying the descending colon is dependent.

Analysis of arteriographic studies shows that anastomosis at Griffiths' point is present in 48 percent, poor or tenuous in nine percent, and absent in 43 percent.

This critical point is of significance in occlusive vascular impairment of the left colon, both in spontaneous instances and following surgical ligation of the inferior mesenteric artery, and in "nonocclusive" ischemic colitis. Its relationship to arteriosclerotic stenoses and low flow states is discussed.

Individuals with absence of dependable anastomoses at Griffiths' point at the splenic flexure may be particularly vulnerable to low perfusion states and develop the syndrome of ischemic colitis.

Complete arteriographic evaluation is necessary in ischemia of the colon. This includes particularly assessment of atherosclerotic changes at or near the ostia of the major visceral arteries and the vascular arrangement at Griffiths' point.

THE classical anatomic descriptions of the blood supply to the left colon do not fully explain the occurrence, distribution, extent, and severity of many vascular disorders of the large intestine. The inferior mesenteric artery (IMA) arises directly from the lower abdominal aorta and gives rise to three main divisions: the ascending left colic (ALC), sigmoidal, and superior rectal arteries. The ALC anatomically reaches the splenic flexure in 86–89 percent of cases[19,34] where it anastomoses with the middle colic artery (MC) which arises from the superior mesenteric artery (SMA). Along its course, the ALC gives off two to six, usually three, branches which anastomose with the marginal artery (MA) of Drummond.[14] The marginal artery is "the functional vessel of the colon."[20] This arterial channel runs along the mesenteric border of the colon at a distance of one to one and a half inches. From it originate the vasa longa and vasa brevia which supply the bowel wall. The sigmoidal arteries vary in number and supply the sigmoid colon. The superior rectal artery is the terminal portion of the IMA and supplies the rectum, where it anastomoses with the middle and inferior rectal arterial ramifications which arise from the internal iliac arteries and their branches. A rich collateral supply, both proximally and distally, is thus associated with the vascularization of the left half of the colon.

In the 1950s the increasing number of operations for aortic aneurysms and high

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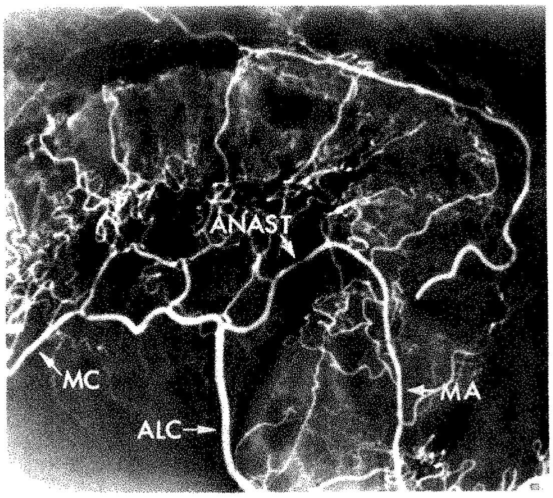

FIG. 1. Injected postmortem specimen of Griffiths' point at the splenic flexure. At its terminal connection with the middle colic artery (MC), the ascending left colic artery (ALC) in this instance is in anastomotic communication with the marginal artery (MA). This arterial link is of relatively narrow caliber.

ligation of the inferior mesenteric artery[22,35] during resections for colonic carcinomas resulted in numerous instances of large bowel ischemia with gangrene, stricture, and colitis.[3,4,42,46,53] The incidence of ischemia of the colon following high ligation of the IMA in surgery of carcinoma of the colon and rectum is reported as 2.4 percent[22] to 22 percent,[18] and after resection of abdominal aneurysms is about ten percent.[46] The spontaneous and reversible nature of some episodes of ischemic colitis was first emphasized in 1963[5,39] and the identification of roentgenologic criteria for its early diagnosis were established.[39,40] It has since been appreciated that both spontaneous acute occlusion limited to the inferior mesenteric artery[8] and "nonocclusive" ischemia of the colon may result in irreversible damage with stricture or gangrene. In all series of ischemic colitis, the splenic flexure is most commonly involved, often with an adjacent segment of the descending colon.[7,28,48] This is frequently explained by the fact that the splenic flexure is at the watershed of a dual blood supply (*via* the ascending left colic branch of the IMA and the middle colic branch of the SMA). However, it is apparent that this is only teleological reasoning, since the same explanation would be applicable if, in contrast, it were empirically observed that the splenic flexure tends to be spared in ischemic colitis. Occasionally, the "spontaneous," nonocclusive episodes of colonic ischemia may be attributed to low flow states from a variety of causes. This may be seen secondary to reduced cardiac output as in cardiogenic shock, arrhythmias, congestive heart failure, and prolonged hemorrhagic hypotension. Mesenteric ischemia may be potentiated by digitalis which produces splanchnic vasoconstriction.[41] In such circumstances, the colonic segment farthest from its arterial source is most susceptible to decrease in blood flow or perfusion pressure. Yet, it is apparent that the precise morphology of the anastomoses specifically contributing to vascularization of the splenic flexure may predispose this segment to the effects of ischemia secondary to either occlusive or low perfusion states.

Faulty paracolic anastomosis between the superior and inferior mesenteric arteries were noted in early isolated observations.[17,45] In a series of 100 autopsies, Robillard and Shapiro[38] observed three instances in which there was either an apparent failure of peripheral major anastomosis between the middle colic and the left colic artery or narrowing of this anastomotic arch to 1–1.5 mm for several centimeters, a dimension inadequate for dependable collateral circulation. Typically, the ascending left colic artery bifurcates at the splenic flexure, its right branch joining the left branch of the middle colic and its left branch joining the marginal artery. In 1956, on the basis of autopsy material, Griffiths[19] reported that "a truly critical point exists, however, at the splenic flexure, where the marginal artery is often small. The left colic artery as it approaches the splenic flexure usually divides about two inches from the gut. One branch passes to the distal loop of the flexure; the other branch goes to the transverse colon, effecting an anastomosis with the left branch of the middle colic artery. The terminal form of the left colic artery should always be preserved after ligation of the inferior mesenteric at its origin, since it forms a second marginal artery, otherwise the distal colon is dependent solely on the very fine marginal artery of the splenic flexure."

We have studied the vascularization of the splenic flexure in fresh postmortem material by injection of the abdominal vessels with a barium-gelatin mixture, *en bloc* dissection, and then roentgenography of the specimens. Figure 1 illustrates the presence of the vital anastomotic connection at Griffiths' point at the splenic flexure.

Griffiths' point was further defined by Michels and associates[33,34] as occurring when the last bifurcation of the ascending left colic occurs at some distance (3–7 cm, average 5 cm) from the splenic flexure. In such cases the right and left branches of the ascending left colic artery are not anastomosed and, therefore, function as the marginal artery of Drummond. In their autopsy specimens, continuity of the marginal artery at the splenic flexure, that is, anastomosis between the right and left branches, was substantial and adequate in 61 percent, tenuous in 32 percent, and absent in seven percent (Fig. 2). Griffiths,[20] however, thought that this critical point is "of no significance except after ligation of the inferior mesenteric artery during operative procedures on the distal colon and rectum, when the main blood supply to the distal colon will be *via* the marginal artery from the middle colic branch of the superior mesentric artery. In these cases it is imperative to see that the bifurcation of the left colic artery is left intact, to ensure a secondary arcade for the marginal artery in this area."

From a functional point of view, we prefer to broaden the definition of Griffiths' point to include: (1) communication of the ascending left colic artery with the marginal artery of the descending colon at the splenic flexure; and (2) anastomotic bridging between the right and left terminal branches of the ascending left colic artery.

Reported arteriographic observations of the inferior mesenteric artery and its tributaries to the left colon have not detailed this critical point. Analysis of a series of 136 aortograms and selective inferior mesenteric arteriograms by Kahn and Abrams[24] shows the segments of the colon supplied by the inferior mesenteric artery. In about 45 percent, the IMA supplies the descending colon but does not include the splenic flexure. In 44 percent, the splenic flexure is included in the area of supply, and in an additional ten percent the branches extend proximal to the splenic flexure. In only three percent of the cases is the mid-transverse colon supplied by the IMA, the overwhelming majority demonstrating sup-

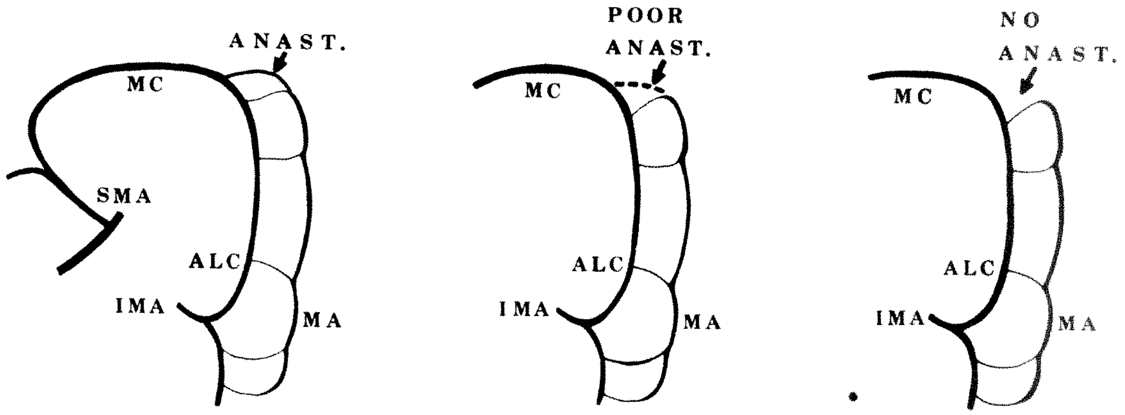

FIG. 2. Griffiths' critical point. Anastomosis may be substantial, tenuous, or absent.

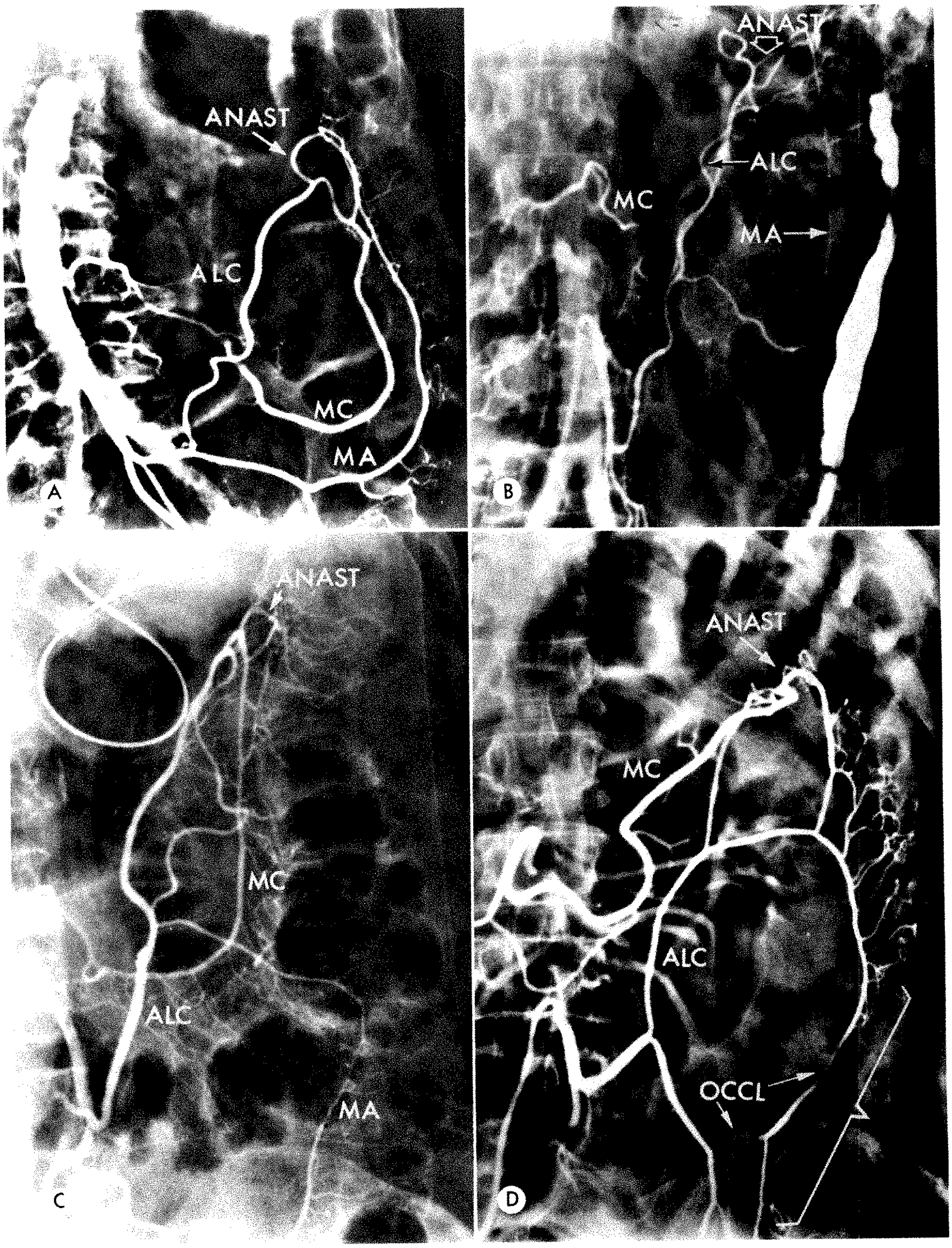

FIG. 3. (*A–D*) Substantial marginal communication at Griffiths' critical point at the splenic flexure, demonstrated by selective inferior mesenteric arteriography in four patients. Anastomosis is clearly identifiable connecting the marginal artery of the descending colon with the terminal portion of the ascending left colic artery as it branches to join the middle colic artery.

In an asymptomatic patient (*D*) there are also occlusion of a sigmoid branch and stenosis of a segment of the marginal artery, with localized lack of filling of the vasa recta (bracket).

ply by the middle colic branch of the SMA. While not noted in the report by Kahn and Abrams,[24] their arteriographic illustrations frequently demonstrate absence of the anastomotic marginal channel at Griffiths' point.

The purpose of this report is to: (1) determine the identification and incidence of Griffiths' point *in vivo*, as shown by arteriography; (2) document its relationship to occlusive vascular impairment of the left colon, in both spontaneous instances and following surgical ligation of the inferior mesenteric artery; and (3) establish its significance in "nonocclusive" ischemic colitis.

METHOD AND MATERIAL

In a series of fresh autopsy material, the superior and inferior mesenteric arteries were manually injected *in situ* with a warm barium-gelatin mass. After *en bloc* dissection of the colon with its mesocolon and formalin fixation, roentgenography of the injected specimens was accomplished using both whole colons with conventional roentgenographic techniques as well as sections of the splenic flexure with industrial film and the Faxitron roentgenographic unit employing a focal spot of 0.5 cm.[2] Photographic enlargement then highlighted some details.

Fifty-eight selective inferior mesenteric arteriograms with serial filming were reviewed. In 22 of these cases, selective superior mesenteric arteriography had also been performed and was available for review. Percutaneous transfemoral catheter insertion was employed in all cases. Redundancy of the splenic flexure with crowded superimposition of its arterial branches or poor overflow opacification in the absence of significant ostial stenosis made detailed angiographic analysis of the vascularization impossible in some instances. Satisfactory, clear visualization of the arterial ramifications at the splenic flexure was achieved in 46 selective inferior mesenteric arterial studies and eight selective superior mesenteric arteriograms. Opacification of the middle colic artery was seen on the IMA studies and of the ALC and MA on the SMA studies.

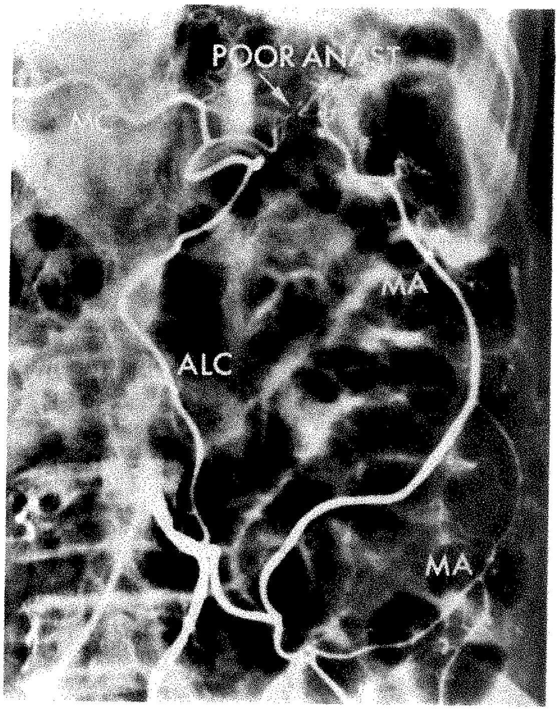

Fig. 4. Very tenuous communication at Griffiths' point. Selective inferior mesenteric arteriogram demonstrates minute and probably incomplete ramifications bridging the ascending left colic and marginal areries at the splenic flexure.

Selected clinical cases of ischemia of the colon were reviewed and their roentgenographic, arteriographic, and pathologic features analyzed.

ANALYSIS OF VASCULARIZATION AT THE SPLENIC FLEXURE

On the postmortem injection studies, even if an anastomosis provided communication at the splenic flexure between the ascending left colic artery and the marginal artery of the descending colon, it was frequently of narrower caliber than either of these two vessels (Fig. 1).

Detailed identification of the vascularization of the splenic flexure *in vivo* was possible in the 46 patients with selective arteriograms suitable for analysis. Anastomotic connection at Griffiths' point was present in only 22 (48 percent) (Fig. 3, *A–D*). In these patients, there was con-

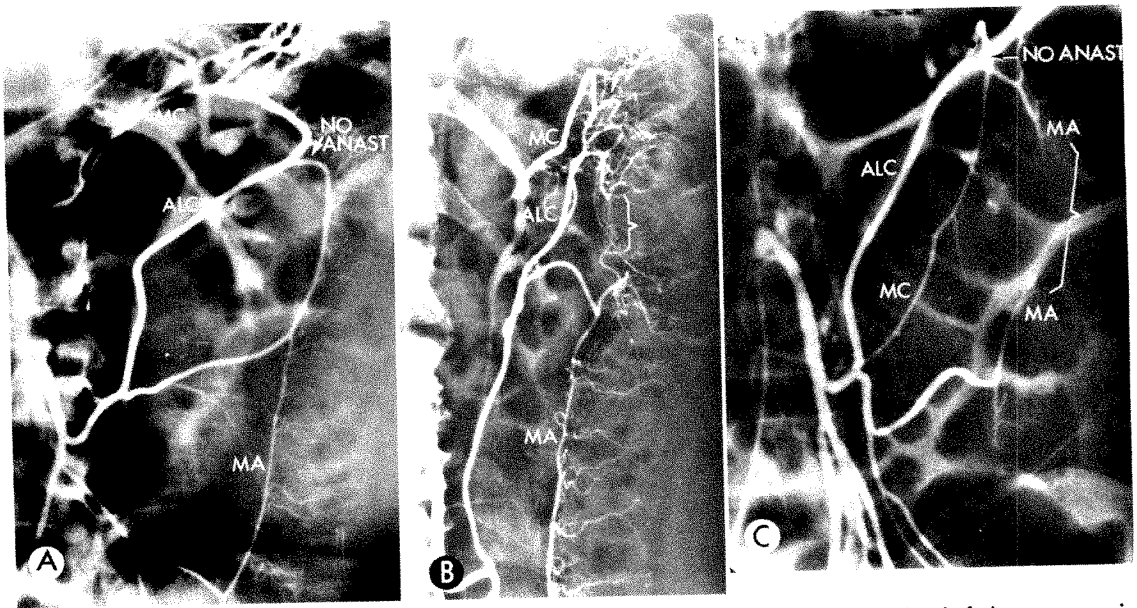

FIG. 5. (*A–C*) Absent anastomosis at Griffiths' critical point, demonstrated by selective inferior mesenteric arteriography in three patients. No vessel bridges the right and left terminal branches of the ascending left colic artery. Communication is established with the middle colic artery and the marginal artery of the descending colon, but there is no anastomotic marginal channel distal to the bifurcation of the ascending left colic artery. In both (*B*) and (*C*), there is also localized discontinuity of a segment of the marginal artery near Griffiths' point, with no filling of the vasa recta (brackets).

tinuity of the marginal artery at the splenic flexure, that is, anastomosis between the ALC and the MA or arterial bridging between the right and left terminal branches of the left colic artery. Anastomosis at Griffiths' point was poor or tenuous in four (nine percent), being constituted by very small bridging ramifications (Fig. 4). No anastomosis was present in 20 cases (43 percent) (Fig. 5, *A–C*; and 6), with the discontinuity in the marginal arterial channel of the splenic flexure often extending over several centimeters.

OCCLUSIVE VASCULAR IMPAIRMENT OF THE LEFT COLON

Ischemia of the left colon may vary: (1) in degree, from edema to infarction; (2) in extent, from localized to more generalized involvement; and (3) in the nature of the major supplying arterial bed, from occlusive (spontaneous or following surgical ligation of the IMA) to "nonocclusive."[28,52]

Demos[11] has reviewed 50 cases from the literature of IMA occlusion with extensive vascular impairment of the left colon. Thrombotic occlusions may be precipitated by surgical ligation,[2,3,42,46] atheromatous plaques,[2,8,23,30] saccular aortic aneurysms,[8] retroperitoneal hematoma from leaking aneurysms,[30,46] aortography, blood dyscrasias, sepsis, and splenectomy.[8] Clinically, such patients are characterized by the onset of sudden, severe lower abdominal pain, tenderness, rigidity and bloody rectal discharge.[8] Barium enema findings (Fig. 7) usually show the descending colon from the splenic flexure to at least the rectosigmoid to be contracted, with edematous nodular mucosal thickening. Progressive slough of the mucous membrane may present bizarre, irregular filling defects, and multiple ulcers may be identified.[15,30] On sigmoidoscopy, the necrotic mucosa appears bluish black.[2,8,9,46]

A less fulminating course may permit the infarcted segment to progress to an ischemic stricture. We have had the opportunity to observe this in a unique sequence of surgical interventions. A 69 year old female underwent resection of the splenic flexure for carcinoma in 1968, and then resection of the sigmoid colon for carcinoma in 1973. Obstipation, abdominal cramps and weight loss led to another barium enema study three months after the second operation (Fig. 8). This documented the presence of a long ischemic stricture involving the descending colon which required a left colectomy and end-to-end anastomosis between the proximal transverse colon and the rectal stump. This case can be likened to an experimental model *in vivo* in that surgical removal of the anastomotic communications at Griffiths' point was followed five years later by high ligation of the IMA. Patency of the internal iliac arteries was not interfered with. Sequential deprivation of the critical blood supply of the left colon led inexorably to an ischemic stricture.

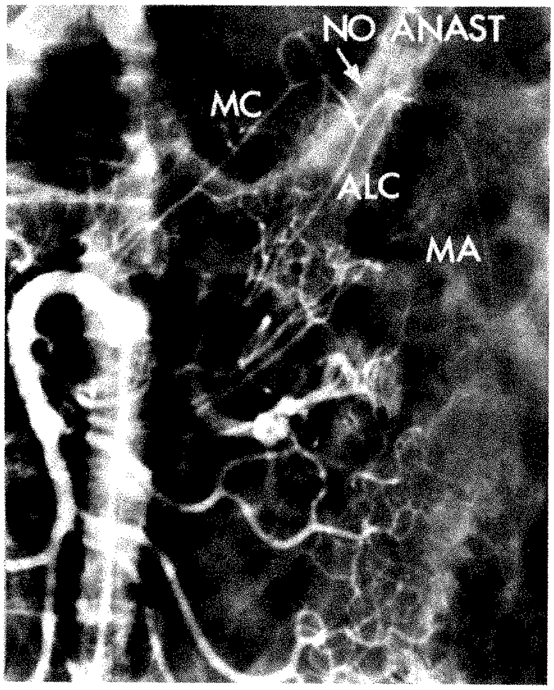

FIG. 6. Absent anastomosis at Griffiths' point, demonstrated by selective superior mesenteric arteriography. Retrograde opacification of the ascending left colic, *via* the middle colic branch of the superior mesenteric artery, shows lack of marginal anastomosis bridging its terminal branches at the splenic flexure.

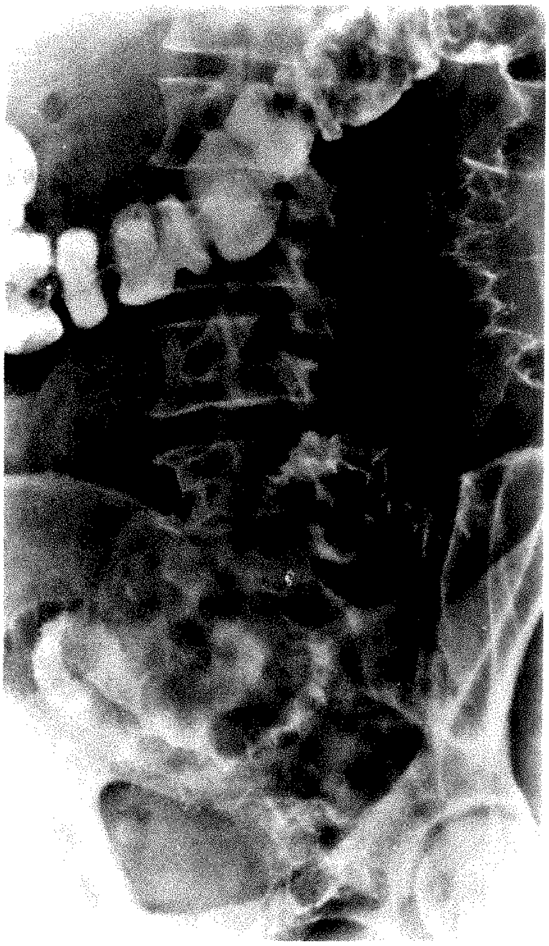

FIG. 7. Acute thrombosis of inferior mesenteric artery with infarction of descending colon, in a 56 year old man recovering from an acute myocardial infarction. The entire left half of the colon from the splenic flexure to the rectum shows marked contraction with grossly edematous mucosal thickening. This localized nodular character often presents as "thumb-print" defects. Resection of the infarcted segment revealed that acute thrombosis extended throughout the arterial branches.

We have noted that occlusive infarction or gangrene of the colon may be manifested by striking dilatation, rather than contraction. Figure 9, *A* and *B*, illustrates this in the sigmoid colon following resection of an abdominal aneurysm. The IMA is frequently occluded at the time of operation in abdominal aneurysms[10,46] but even if not, it must nevertheless be sacrificed. It is apparent that collateral channels may not be

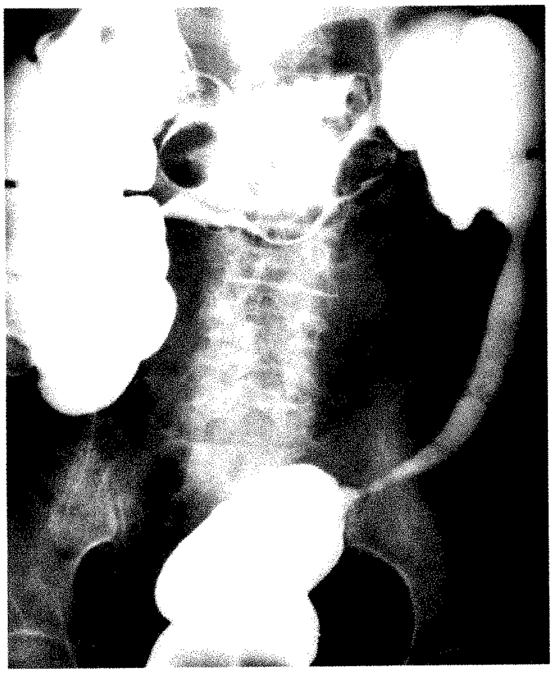

FIG. 8. Ischemic stricture of descending colon following segmental resections of splenic flexure and sigmoid colon. Rigid narrowing is the consequence of loss of the anastomoses at Griffiths' point and of high ligation of the inferior mesenteric artery.

adequate to maintain viability. Figure 10, *A–G*, illustrates necrotic dilatation of the descending colon from the splenic flexure to the rectosigmoid in a patient with not only occlusion of the inferior mesenteric artery but also, significantly, demonstrated absence of anastomoses at Griffiths' point.

Significantly, in over one-third of the 50 cases reviewed by Demos,[11] it had been established that in addition to the inferior mesenteric artery, the proximal (SMA) or distal (hypogastric arteries) collateral blood supply was occluded. For example, in five cases of ischemic colitis following IMA ligation, Bernstein and Bernstein[3] recognized ostial narrowing of most of the aortic branches. Apparently, as far as ischemia of the colon is concerned, it does not matter whether the right or the left hypogastric artery becomes occluded.[46] Even temporary clamping of the hypogastric arteries after sacrifice of the IMA for surgery of abdominal aortic aneurysms may produce ischemic damage to the left half of the colon in ten percent of cases.[46] This may range from transient mucosal ulceration to massive gangrene.

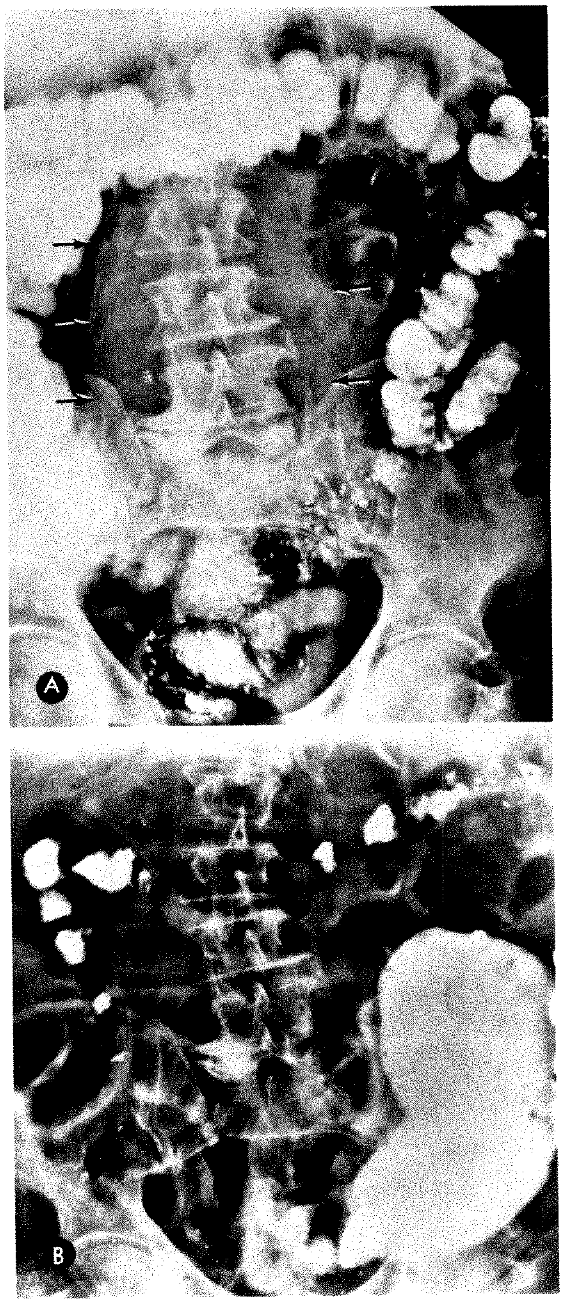

FIG. 9. Gangrene of the sigmoid colon following resection of aortic aneurysm. (*A*) Calcification outlines a huge aneurysm of the abdominal aorta (arrows). Note the residual barium in the colon. (*B*) Following emergency aneurysmectomy, there is massive dilatation of the gangrenous sigmoid colon, within which there is barium stasis.

In two cases,[2,46] IMA ligation had been performed several months to one year previously during aortic surgery, but the colonic gangrene ensued immediately after an operation for correction of a thrombotic episode in the iliac arteries. In one of these,[46] there had been concomitant ligation of an anomalous left colic artery; the marginal arterial link at the splenic flexure was evidently not adequate to prevent the development of necrosis extending from the splenic flexure to the distal sigmoid colon.

That ischemic changes in the left colon may not follow immediately after spontaneous occlusion or high ligation of the IMA is also illustrated by its occasional delayed appearance following abdominoperineal excision of the rectum for carcinoma (Fig. 11, *A* and *B*). Thomas and Wellwood[49] similarly observed the development of ischemic colitis in two patients two and one-half to six years following abdominoperineal resection. No angiographic studies were performed in their cases, but the distribution clearly indicated decreased perfusion in the territory of Griffiths' point.

Kinkhabwala has demonstrated an interesting intersplanchnic steal syndrome operative in a case of ischemia of the large intestine extending from the distal transverse colon to the sigmoid colon. Arteriographic studies demonstrated severe stenosis of the superior mesenteric artery. A markedly enlarged patent inferior mesenteric artery shunted blood from the left half of the colon (Fig. 12) to the SMA *via* the middle colic branch.

ARTERIOSCLEROTIC STENOSES AND "NONOCCLUSIVE" ISCHEMIC COLITIS

In a study of 88 adult patients 28 to 63 years of age, examined as a consecutive unselected postmortem series, Reiner and colleagues[36] found that 77 percent had evidence of atherosclerosis of the mesenteric vessels. Stenosis or occlusion involved the SMA in 39, the IMA in 30, branches of the IMA in 16, and the MC in 14. Severe mesenteric involvement occurs almost exclusively with severe aortic atheroma. Others[27] have found that about one-third of those over the age of 45 years have some atherosclerotic narrowing at the origin of the SMA. An anatomic study by Demos *et al.*[12] reported occlusive disease to be nearly twice as frequent in the IMA as in the SMA.

In the series of 136 aortograms and selective inferior mesenteric arteriograms analyzed by Kahn and Abrams,[24] the IMA was totally occluded in 6.6 percent and significantly stenosed in 17 percent.

Dick *et al.*[13] attempted to estimate the sum of the cross-sectional areas of the celiac, SMA and IMA by lateral lumbar aortography. A significant difference was found in the cross-sectional areas of the group with ischemic bowel disease as compared to a control group. A normal cross-sectional area was established, and in cases of intestinal ischemia the cross-sectional area of the main arterial trunks was reduced by more than one-third.

Yet angiography in "spontaneous" ischemic colitis, whether reversible or progressive, is usually reported as showing no demonstrable vascular occlusion.[37,43,51,52] However, many of the reported cases are based on either abdominal aortograms with only gross demonstration of the major mesenteric vessels or incomplete selective studies. Williams and associates[52] have reported five cases of spontaneously occurring reversible and irreversible ischemic colitis in which there were "no evidence of arterial occlusion by angiography." In four of these, however, evaluation was accomplished only by aortography which showed basically no occlusion of the SMA or IMA. No further information concerning the colic branches, marginal artery, or Griffiths' point is given. In another case, a selective superior mesenteric arteriogram revealed filling of all major branches including the MC and ALC arteries throughout the area of colonic involvement. No mention of the marginal artery or the precise vascularization of the splenic flexure is made. Reuter *et al.*[37] studied two patients during the healing phase of ischemic colitis, both of which progressed to strictures of the splenic

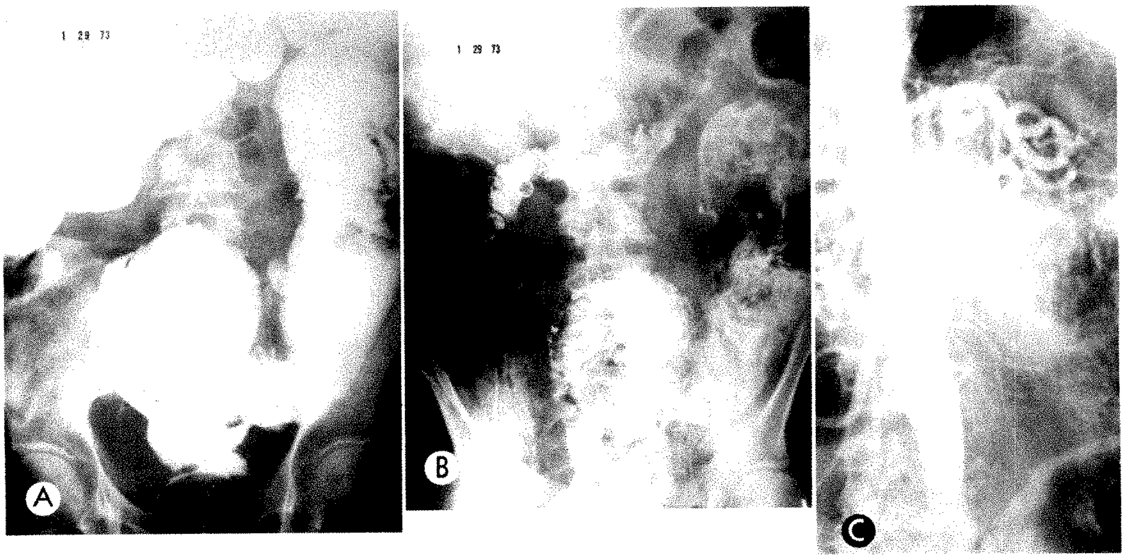

FIG. 10. Infarction of descending colon with occlusion of inferior mesenteric artery and absence of anastomoses at Griffiths' point, in a 68 year old male presenting with abdominal distention, left lower quadrant pain and diarrhea. (*A* and *B*) Barium enema examination with postevacuation study show gross dilatation of descending colon, bizarre filling defects from necrotic debris including sloughed mucosa, and multiple ulcerations. (*C*) Aortogram two days later reveals occlusion of the IMA. Marked arteriosclerotic changes of the iliac arteries were also demonstrated.

flexure. Inferior mesenteric arteriography in one revealed a few small emboli straddling bifurcations of IMA branches, but no occlusion was found. Selective superior mesenteric arteriography in the second case showed the MC to be patent. Again, these investigators give no specific information concerning Griffiths' point, the marginal artery, or evaluation of major ostial stenoses. The findings of hypervascularity and early venous opacification in the involved areas reflect the rapid and intense attendant inflammatory reaction.[37]

We have established by arteriography, including selective studies, that absence of anastomoses at Griffiths' point may play a crucial role in spontaneous ischemic colitis. Indeed, those individuals with a developmental tenuosity or complete absence of marginal arterial communications at the splenic flexure may be particularly vulnerable to the ischemic effects of low perfusion states. In the face of conditions leading to diminished flow, collateral circulation between the superior and inferior mesenteric arterial systems across Griffiths' point at the splenic flexure may simply not be adequate to maintain nutrition. In the age group commonly involved, arteriosclerotic stenoses at or near the ostia of the major vessels further dampen the diminished perfusion pressure peripherally.

Figure 13, *A* and *B*, illustrates the development of ischemic colitis involving the splenic flexure in a 56 year old female with congestive heart failure and paroxysmal atrial fibrillation. Although aortography (including serial lateral views) and selective superior mesenteric arteriography showed no lesions, selective inferior mesenteric arterial studies clearly demonstrate inadequate marginal communications at both sites of Griffiths' point.

Figure 14, *A–E*, illustrates absent anastomoses at Griffiths' point in a case of ischemic colitis occurring proximal to a carcinoma of the sigmoid colon. Whereas dilatation with altered hemodynamics above a partially obstructing lesion may contribute to such a process, diminished vascularization at the splenic flexure appears to underlie the ischemic effects. This case, similar to

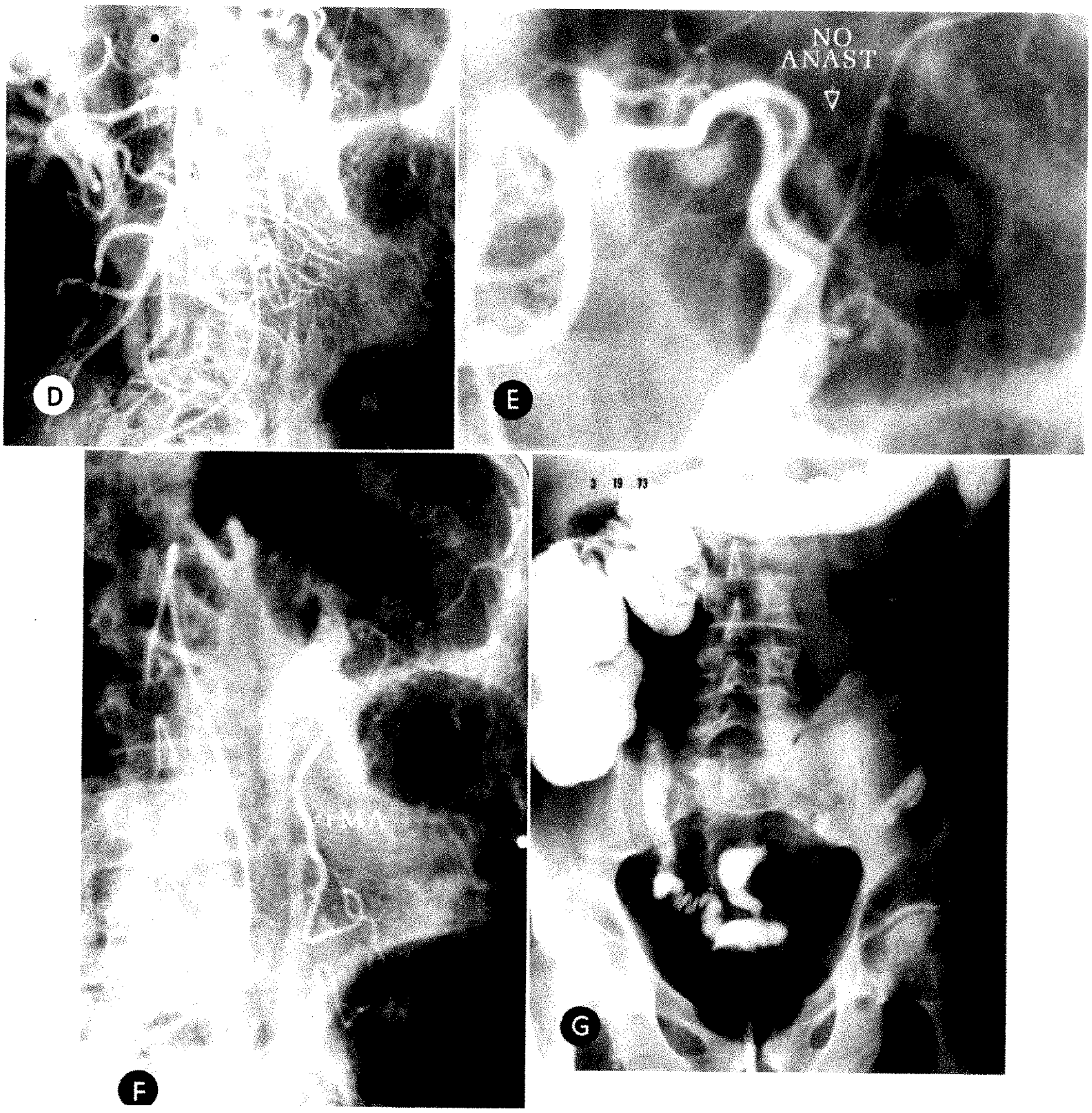

FIG. 10. (*D* and *E*) Selective superior mesenteric arteriograms demonstrate absence of marginal anastomoses at Griffiths' point at the splenic flexure between the middle colic branch and the marginal artery of Drummond. (*F*) Late roentgenogram from SMA study shows retrograde opacification of the marginal artery with faint visualization of the vasa recta. There is absolutely no filling of the ALC or IMA. (*G*) Barium enema examination eleven weeks later shows the progression to a severe ischemic stricture from the splenic flexure to the rectosigmoid.

Figure 8, also shows the importance of Griffiths' point in vascular deprivation of the left half of the colon following high ligation of the inferior mesenteric artery (Fig. 14 *E*).

Unfortunately, occasional reports of positive arteriographic findings in ischemic colitis are often incomplete in evaluation, detail, or in documenting the time of the study in relation to the onset of the process. Sherbon[43] reported an area of "decreased vascularity" on inferior mesenteric arteriography which corresponded to an ischemic bowel segment requiring resection. Aortography in one of the cases reported by Farman[16] revealed IMA occlusion which

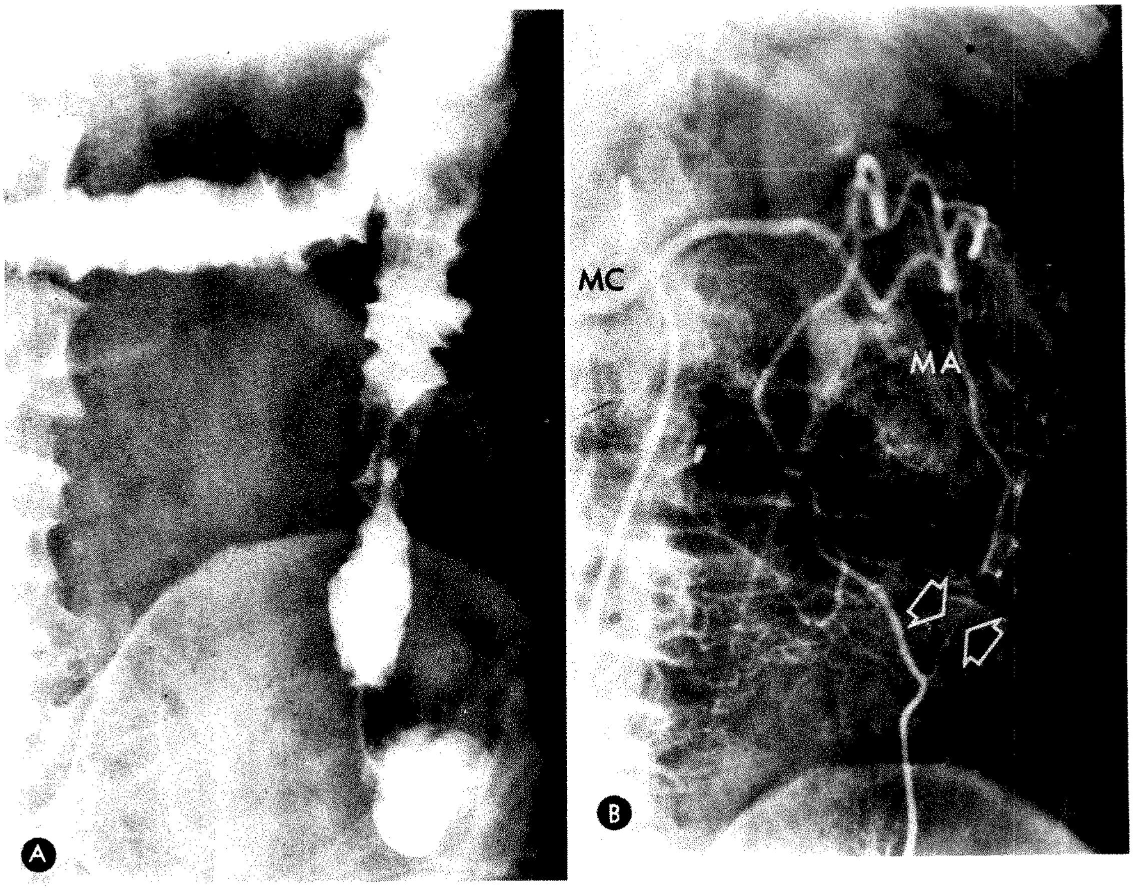

Fig. 11. Ischemic colitis of the splenic flexure after abdominoperineal resection of the rectum. (*A*) Four months following surgery, acute ischemic edema and thumb-print defects involve the distal transverse colon, splenic flexure, and descending colon to the level of the colostomy. (*B*) Selective superior mesenteric arteriogram. Retrograde opacification of the marginal artery *via* the middle colic shows a very tenuous segment (arrows) just distal to the splenic flexure.

presumably accounted for irreversible ischemic changes in the rectum and sigmoid colon. In a recent report by Lambana *et al.*,[25] there is no indication of the date of the selective inferior mesenteric arteriographic findings of branch stenoses and a scanty marginal artery relative to the three month course of the patient's irreversible ischemic colitis.

Other reports, however, indicate the significance of the vascularization at the splenic flexure. Marston and colleagues[28] studied an ischemic stricture of the splenic flexure two to three months after onset by aortography which showed no middle colic artery and no anastomosis between the superior and inferior mesenteric systems at the splenic flexure. Shippey and Acker[44] studied a patient with ischemic colitis involving the splenic flexure and descending colon by selective inferior mesenteric arteriography eleven days after hospitalization and demonstrated occlusion (probably embolic) of the ALC distally near the splenic flexure, as well as marked narrowing of the ostium of the IMA. Resection was done because of the development of a fibrotic stricture, and a tenuous marginal artery was identified in the specimen. In a patient with ischemic colitis extending from the distal transverse colon to the proximal sigmoid colon, Westcott[50] demonstrated complete occlusion of the ALC (probably embolic) just distal to its origin with no arterial filling of the vessels supplying the splenic flexure. The colonic changes of segmental narrowing, edema, and "thumb-printing" completely resolved.

DISCUSSION

Despite the fact that a dual blood supply serves the splenic flexure of the colon, a critical point is established by continuity of the marginal artery at this site between the superior and inferior mesenteric arterial systems. It is upon this point that collateral circulation may become dependent. From a functional view, we have defined it as the areas of communication of the ascending left colic branch with the marginal artery of the descending colon at the splenic flexure and of anastomotic bridging between the right and left terminal branches of the ascending left colic artery. Study of arteriographic examinations *in vivo* provides a more realistic physiologic and anatomic analysis than postmortem investigations alone. Our series has shown that Griffiths' point is tenuous or absent in 52 percent. Clinical experience has shown repeatedly that the inferior mesenteric artery may be ligated or removed with im-

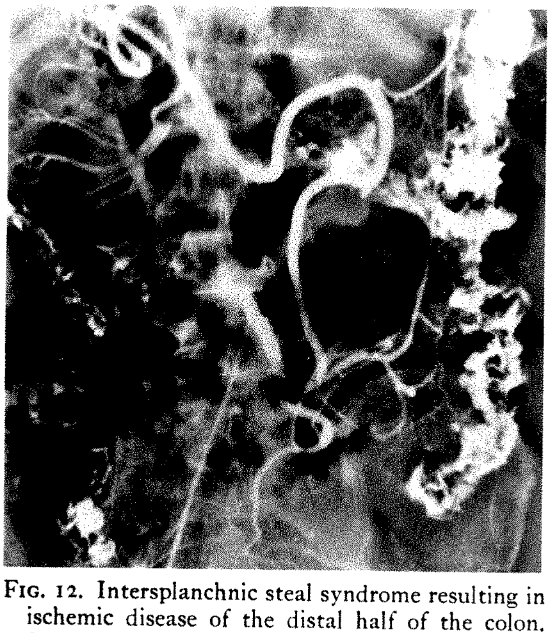

Fig. 12. Intersplanchnic steal syndrome resulting in ischemic disease of the distal half of the colon. Selective inferior mesenteric arteriogram demonstrates that the flow of blood in this situation, with severe stenosis of the SMA, is diverted from the left colon by the middle colic branch.

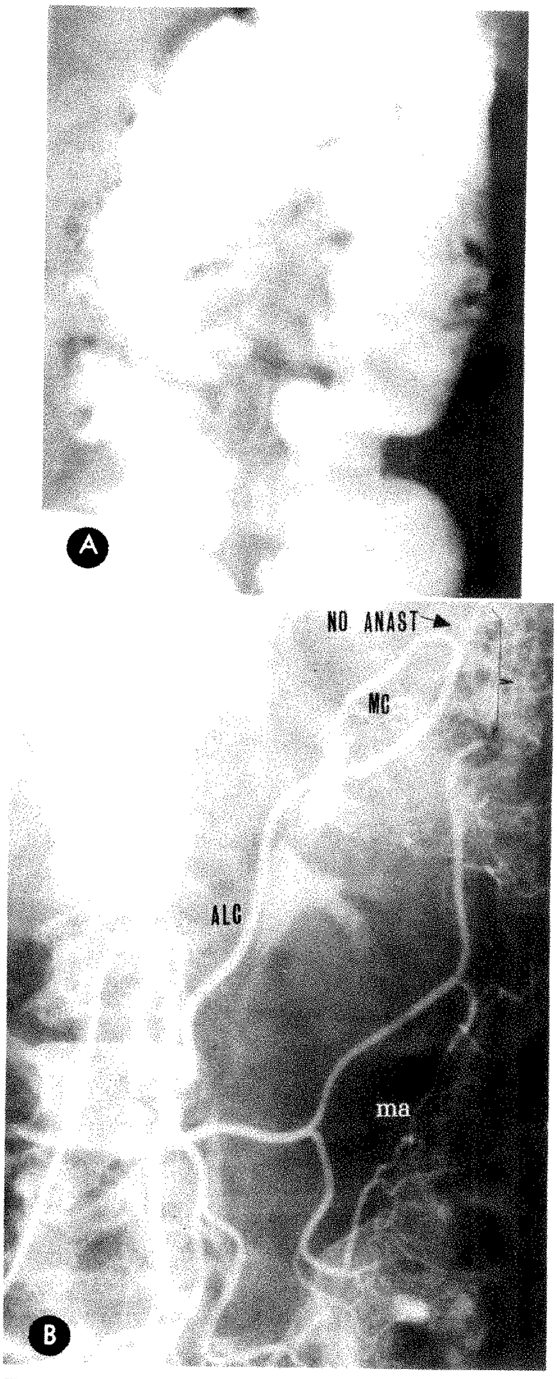

Fig. 13. Absent anastomosis at Griffiths' point underlying nonocclusive ischemic colitis. (*A*) Spot roentgenogram of splenic flexure shows edematous mucosa and thumb-print defects. (*B*) Selective inferior mesenteric arteriogram. At the splenic flexure, there is no anastomosis bridging the right and left terminal branches of the ascending left colic artery. Furthermore, there is localized absence of communication between the ALC and the marginal artery at the splenic flexure (bracket).

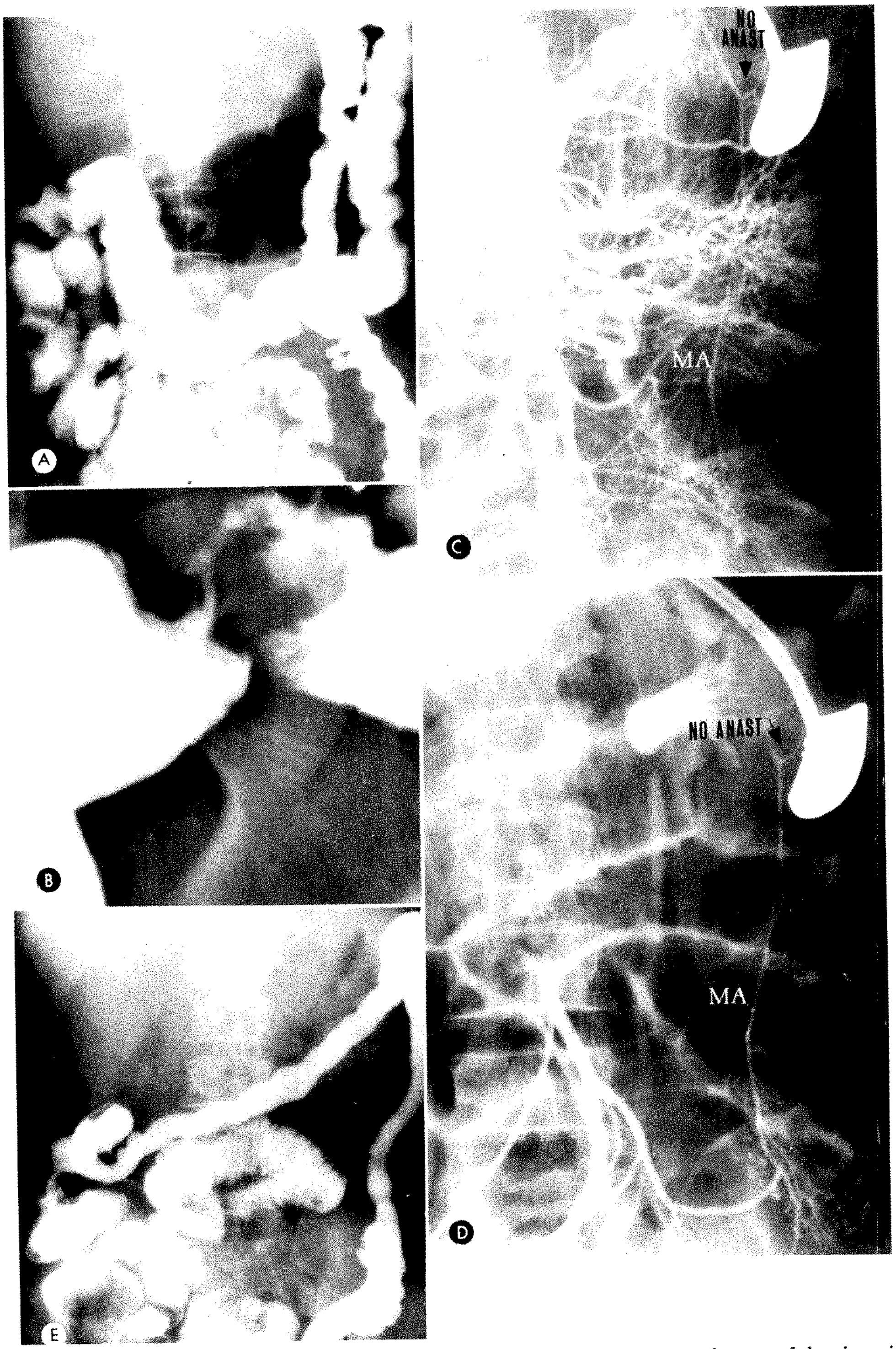

Fig. 14. Absent anastomosis at Griffiths' point in ischemic colitis proximal to carcinoma of the sigmoid colon. (*A* and *B*) Barium enema studies show edematous mucosa and thumb-print defects most prominently in sigmoid colon, splenic flexure, and transverse colon. These changes are proximal to a carcinoma of the sigmoid colon. Three days later, selective superior (*C*) and inferior (*D*) mesenteric arteriograms demonstrate absence of anastomotic communication at Griffiths' point. Note the developmental absence of the ascending left colic artery as well. (*E*) Three weeks after sigmoid resection with high ligation of the inferior mesenteric artery, there is a stricture of the large intestine from the distal ascending colon to the distal descending colon.

punity, and yet at times its occlusion will give rise to infarction of the descending colon. When this happens, a frequent finding noted in the past has been an impairment of the anastomotic circulation, involving the superior mesenteric artery[11,30,42] or internal iliac arteries.[11,46] Arteriosclerotic disease of the major vessels contributing to the collateral vascularization of the left half of the colon undoubtedly plays a role, but does not appear to be the major factor. The inferior mesenteric artery itself is significantly stenosed or occluded in 24 to 34 percent of individuals.[24,36] Without other superimposed conditions, functional and structural viability of the left colon is maintained. In 1907, Sudeck[47] described a critical point in the anastomosis between the superior rectal artery and the last sigmoid artery, and considered the marginal artery to be absent in this region. Its presence or absence, exact position, and clinical significance have occasioned considerable confusion and disagreement. More recent injection experiments have demonstrated that this anastomosis is always adequate, and that Sudeck's critical point is devoid of surgical or anatomical importance, representing, indeed, nothing more than a false conclusion based upon the inadequate injection of too small a series.[19,31] It has been shown that the middle rectal artery is capable of supplying the distal segment of the colon or rectum, following ligation of the inferior mesenteric artery.[35] In contrast to the colonic arteries, which form anastomosing arcades before penetrating the intestinal wall, the branches of the rectal arteries do not form arcades but enter the intestinal wall directly and independently[34] where they form rich intramural anastomotic channels.[31]

In the transverse colon, the middle colic branch of the superior mesenteric artery serves as the marginal artery in that it gives rise to the arcades and vasa recta. At the splenic flexure, it almost invariably has a substantial anastomosis with the ascending left colic branch of the inferior mesenteric artery, either directly or at least with its right terminal branch. The morphology of the vascular links at this site, Griffiths' point, in establishing or not fulfilling collateral continuity with the marginal artery of Drummond supplying vasa recta to the descending and sigmoid colon, is of crucial importance.

Griffiths' point thus appears to be of critical significance not only in acute occlusion of the inferior mesenteric artery but in many cases of spontaneous ischemic colitis as well. Discontinuity of the marginal artery at the splenic flexure is present, on a developmental basis, in about half of all individuals. In an aged patient with some degree of arteriosclerotic stenoses, the splenic flexure of the colon is then particularly vulnerable to the effects of a low flow state of any nature. It is the segment most peripheral to the diminished perfusion pressure and subject to the effects of ischemia. In the absence of communications between the marginal artery of Drummond and the ascending left colic-middle colic system at the splenic flexure, there is no dependable collateral circulation with low perfusion states. It must be emphasized that proximal to the rectum there is a very poor circulation between the vasa recta, and despite the richness of the submucosal plexus, it is too narrow in caliber to allow the development of any extensive intramural collaterals.[20] The marginal artery itself may be segmentally discontinuous near the splenic flexure with no identifiable filling of the vasa recta. This further makes this area vulnerable to ischemia when no anastomosis exists at Griffiths' point (Fig. 5, *B* and *C*).

Complete arteriographic evaluation is necessary in cases of ischemia of the colon. Aortography with biplane studies permits assessment of the orifices of the celiac, superior mesenteric and inferior mesenteric arteries as well as visualization of the internal iliac arteries. Selective studies of the SMA and IMA then allow detailed analysis, in particular including the morphology of Griffiths' point and the preferential flow in the marginal artery. This information is invaluable in understanding the etiology and mechanism of both occlusive and spontaneous, "nonocclusive" ischemic colitis. It may, furthermore, permit some predictability of prognosis. In particular, ischemic colitis occasioned by low perfusion states may be prone to some degree of irreversibility, *e.g.*, stricture formation, in the absence of anastomoses at Griffiths' point.

Comprehensive arteriographic examination also permits evaluation of normal vascular variants. The middle colic artery is absent in three percent[33] to 22 percent.[19] In such cases, the ALC is unduly large and its terminal branches extend into the transverse mesocolon. The splenic flexure may be supplied by an accessory middle colic artery derived from the celiac trunk or its hepatic or splenic branch.[34] The ascending left colic artery is completely absent in six percent[19] (Fig. 14 *D*). Occlusion of all three splanchnic vessels without signs or symptoms of bowel ischemia is possible.[29] There is an extensive undelimited retroperitoneal plexus of Turner with a tremendous potential for the development of collateral circulation in cases of gradual arterial occlusion.[29,33]

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ANGIOGRAPHY AND ULTRASONOGRAPHY*

A COMPARATIVE STUDY OF ABDOMINAL AORTIC ANEURYSMS

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ABSTRACT:

Ultrasound is presently the diagnostic procedure of choice in pulsatile abdominal masses. The ease and accuracy of this method have many advantages over aortography, and ultrasonography can accurately define the size of an abdominal aortic aneurysm. In addition, a normal aorta with an overlying mass, or a tortuous aorta which feels unusually prominent, can be detected, and aortography may not be necessary. Although ultrasound can detect involvement of iliac arteries, it does not allow assessment of the position of the aneurysm relative to the renal arteries, or detect involvement of other branch vessels of the aorta. Ultrasound is more accurate than clinical examination, plain roentgenography, aortography, or isotope aortography in the diagnosis of abdominal aortic aneurysms.

THE definitive diagnostic study for aneurysms of the abdominal aorta has classically been aortography by the translumbar or percutaneous catheter technique. Although in the majority of cases this technique will establish the diagnosis and define the extent of the aneurysm, there are several problems involved in using aortography routinely.

Because most abdominal aortic aneurysms contain laminated thrombus lining the wall, aortography may significantly underestimate the maximum diameter of a non-calcified aneurysm. Secondly, aortography is an invasive procedure, and carries some risk as a routine procedure. On the other hand, it has the advantage of being able to define the relationship of the aneurysm to the renal arteries, to establish involvement of the iliac arteries, and to detect severely stenosed or occluded vessels and collateral circulation which may require correction at surgery. In order to assess the feasibility of eliminating aortography in patients with abdominal aortic aneurysms, we have routinely studied these patients with both aortography and ultrasonography.

METHOD

All patients referred to the angiography laboratory with a suspected abdominal aortic aneurysm were included in the study. In most cases, patients were studied by ultrasound prior to aortography, and in the latter part of the study ultrasound was used as a screening procedure for aortography.

All ultrasound studies were performed with a Unirad gray tone ultrasound unit with a 2.25 megaHz transducer. Mineral oil was applied to the skin to eliminate air between the transducer and the skin. Gray tone scans were recorded by Polaroid films or 70 mm roll film in both the longitudinal and transverse dimensions. Echo-free areas on the gray tone display are verified by A-mode. The A-mode will show an echo-free space between two prominent spikes which oscillates with the pulse, thereby confirming that the aorta is being recorded. Appropriate gain settings were determined by A-mode so that reverberations would not artifactually increase the aortic wall thickness and decrease the lumen size. Gray tone sensitivity settings were varied to optimally display the aorta

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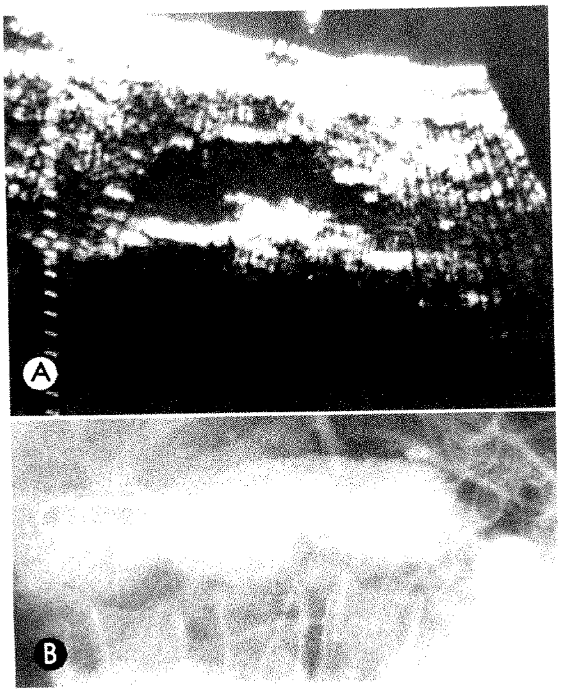

Fig. 1. (*A*) Lateral sonogram demonstrates a lobulated abdominal aortic aneurysm. (*B*) Lateral abdominal aortogram demonstrates an identical configuration of the lobulated aneurysm.

and associated thrombus within an aneurysm. Only the outer wall of the aorta is seen with low sensitivity settings, whereas the higher sensitivity settings will show echoes from intraluminal thrombus. The remaining lumen of the aorta filled with blood will remain echo-free at the higher sensitivity settings. Since aneurysms may not be symmetrical, it is essential to scan them in both the longitudinal and transverse dimensions to determine the maximum diameter.

Aortography was performed by the percutaneous catheter technique, in most cases by the femoral approach, but occasionally through a left transaxillary approach. Two separate injections in the anteroposterior and lateral projections were recorded on a Franklin rapid film changer.

The ultrasound study and aortogram were then compared with reference to the configuration and dimension of the aneurysm. We also attempted to assess the reliability of ultrasound in detecting extension of aneurysms into the iliac arteries. In cases in which the plain abdominal roentgenograms showed calcification, measurements of the calcification of the aneurysm were used as a third indicator in assessing the accuracy of ultrasound and aortography in defining the diameters of aneurysms. Any aortic diameter over 3 cm was defined as an aneurysm.

RESULTS

Thirty consecutive patients referred to the angiographic laboratory with pulsatile abdominal masses were included in this study. In 15 patients, the ultrasound study showed an abdominal aortic aneurysm which was greater than 3 cm in diameter. In all 15 patients, the angiogram confirmed the presence of an aneurysm. The two studies showed a similar configuration of the abdominal aorta in most cases (Fig. 1, *A* and *B*). In eleven of these 15 patients, the diameter of the aneurysm as measured on the ultrasound scan and angiogram correlated well. In four patients, the ultrasound scan demonstrated an aneurysm which was larger than that recorded on the aortogram, presumably due to intraluminal clot which could not be detected by aortography (Fig. 2, *A–D*). In addition, the configuration of the aneurysm on the ultrasound scan compared better with the calcification on plain film than it did with the configuration of the aorta on aortography (Fig. 3, *A–C*).

In 15 patients, the ultrasound study showed a normal aorta. Five of these patients had normal aortograms (Fig. 4, *A–C*) and one showed an ulcerated plaque which had not been detected by ultrasound. This patient did not have an aneurysm, however. In one patient, catheterization was being performed when the patient developed an acute myocardial infarction with cardiac arrest, and no roentgenograms were obtained. He was satisfactorily resuscitated and has since been discharged from the hospital. Aortography in the remaining eight patients was cancelled after the sonogram showed a normal aorta.

DISCUSSION

An abdominal aortic aneurysm must be considered in any patient with a pulsatile abdominal mass. Clinically, diagnosis may be difficult in thin patients who have unusually prominent aortas, or in patients who have masses adjacent to the aorta which transmit pulsations. Some diagnostic test, other than clinical examination, therefore, is required to establish the diagnosis of an abdominal aortic aneurysm.

Plain roentgenograms of the abdomen will show calcification of abdominal aneurysms in 55–85 percent of patients.[9] Since the calcification is in the wall of the aneurysm and outside any thrombus within the lumen, measurement of the calcification will give an accurate measurement of the

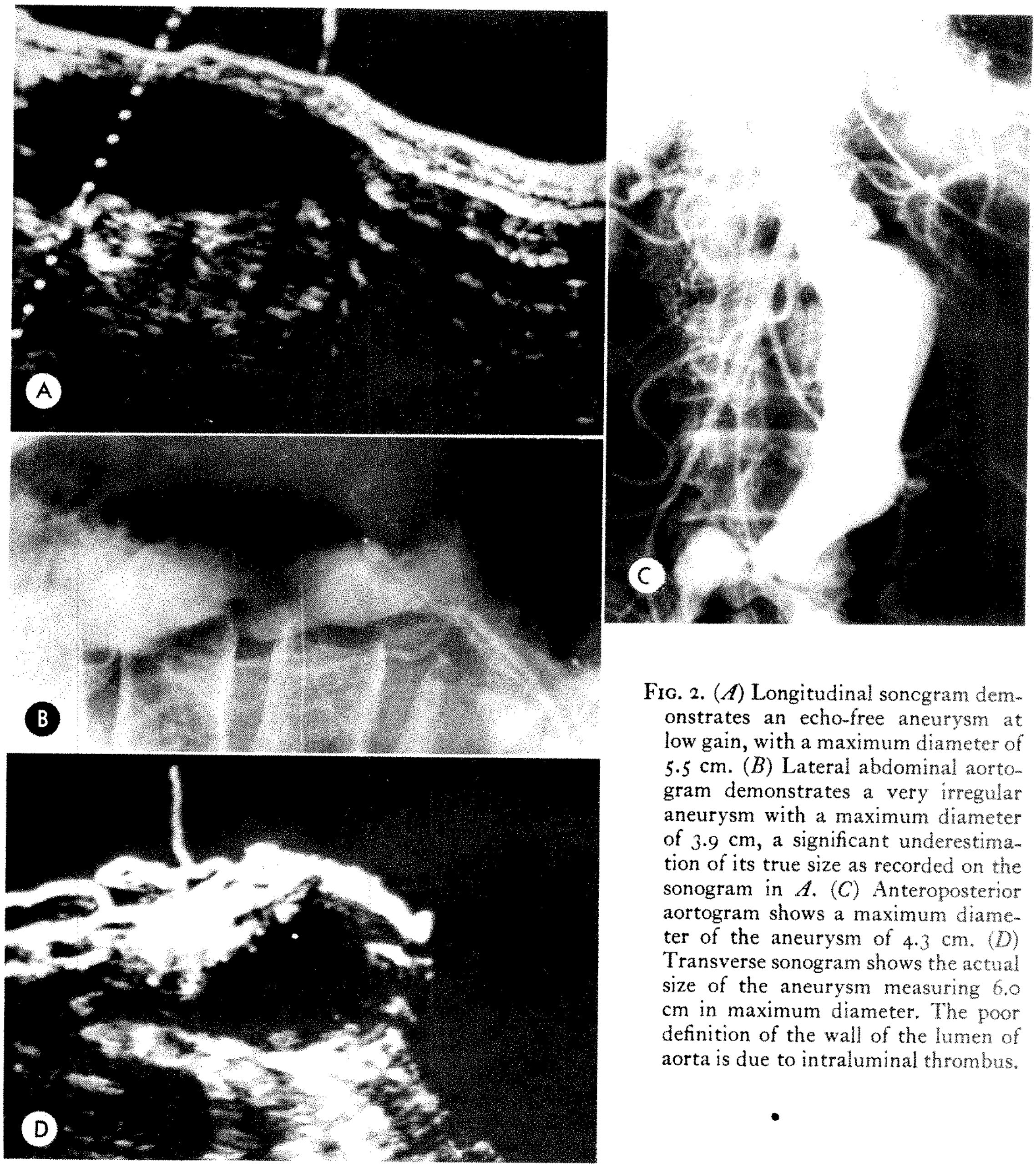

Fig. 2. (*A*) Longitudinal soncgram demonstrates an echo-free aneurysm at low gain, with a maximum diameter of 5.5 cm. (*B*) Lateral abdominal aortogram demonstrates a very irregular aneurysm with a maximum diameter of 3.9 cm, a significant underestimation of its true size as recorded on the sonogram in *A*. (*C*) Anteroposterior aortogram shows a maximum diameter of the aneurysm of 4.3 cm. (*D*) Transverse sonogram shows the actual size of the aneurysm measuring 6.0 cm in maximum diameter. The poor definition of the wall of the lumen of aorta is due to intraluminal thrombus.

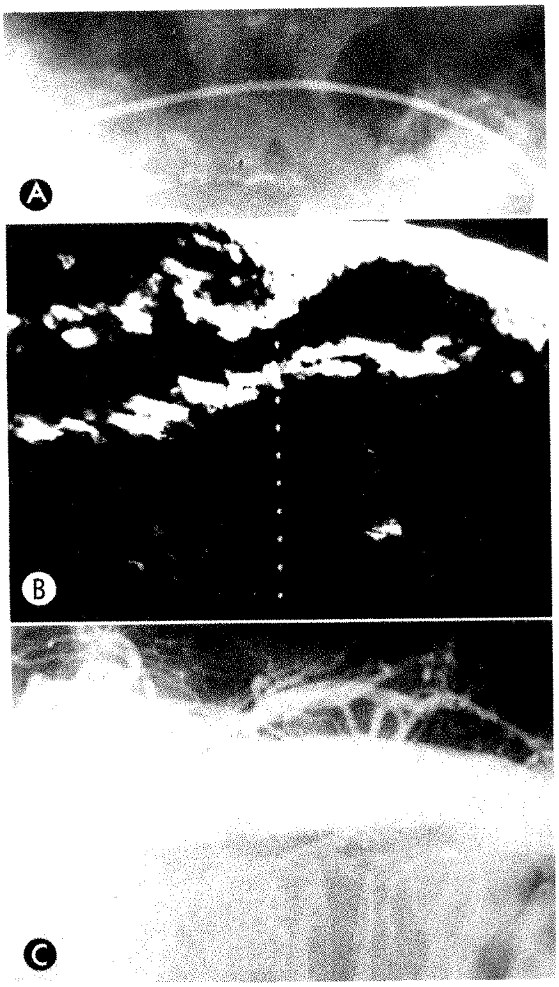

FIG. 3. (*A*) Lateral view of the abdomen with a catheter in the aorta shows calcification lining the wall of an abdominal aortic aneurysm. (*B*) Longitudinal sonogram demonstrates an abdominal aortic aneurysm with a shape identical to that shown by the calcification seen in *A*. (*C*) Lateral aortogram shows dilatation of the aorta, but does not demonstrate the prominent aneurysm seen in *A* and *B*.

size of an aneurysm. This may be measured on the anteroposterior or lateral view of the abdomen. Aortography as a routine study in the evaluation of calcified aneurysms has been abandoned by most surgeons.[1]

In the absence of calcification, the classic approach has been to perform contrast material injections through catheters. This will define the relationship of the aneurysm to the renal arteries, demonstrate the lumen of the aneurysm, show involvement of branch vessels, or reveal stenoses or occlusions related to generalized atherosclerosis. It may provide false negative studies, however, because of the laminated thrombus which may line the lumen of the aneurysm. This may be a serious error because the risk of rupture of an aortic aneurysm is directly related to its diameter.

Patients with an abdominal aortic aneurysm 6 cm or less in diameter have a 75 percent one year survival and a 47.8 percent five year survival.[10] The incidence of rupture is four percent.[3,4] On the other hand, patients with an aneurysm larger than 6 cm have only a 50 percent one year survival, 25 percent two year survival, and a six percent five year survival. The probability of the aneurysm rupturing is 43 percent.[10] When the aneurysm exceeds 7 cm in diameter, the incidence of rupture is from 60 to 82 percent.[2,4,5]

Isotope aortography has been performed in some centers with good results.[1] Injection is made into a peripheral vein, and rapid sequence gamma camera images are recorded over the abdominal aorta. This is a valuable screening procedure, but is not one in general use, and has the same limitations as aortography.

By far the easiest, and probably most accurate method of evaluation of abdominal aortic aneurysms is ultrasonography.[6,11] This is a non-invasive approach, and the study can be performed in less than 20 minutes. A significant advantage of ultrasonography is its ability to define accurately the wall of an aneurysm and therefore give an accurate measurement of its diameter. Leopold *et al.*[8] have found an accuracy in measuring abdominal aneurysms of ±3 mm. Echoes will be returned by laminated thrombus lining the wall of the aneurysm, so that not only can the outer wall and the remaining lumen be defined by ultrasonography, but the presence and position of laminated thrombus in the internal aspect of the aneurysm can be determined. Scanning caudad to the bifurcation of the aorta will, in most cases, show the iliac arteries, and detect aneurysms involving these vessels.[11] Ultrasound is unable to relate the aneurysm to the renal arteries, but since over 90 percent of abdominal atherosclerotic aneurysms originate below the renal arteries, this is not a great problem. Those aneurysms arising above the renal arteries are palpated quite high in the epigastrium and are clinically suspected to involve renal or other visceral vessels. Furthermore, involvement of the renal arteries detected at laparotomy does not prevent surgical correction.

Of equal importance is the ability of ultrasound to detect a normal aorta in patients where either transmitted pulsations through an abdominal mass, tortuosity of the aorta, or the body habitus gives the clinical suspicion of an aneurysm. In these cases, aortography is not necessary because ultrasound is an accurate screening procedure. This is particularly valuable in older patients who are poor risks. In the former case in which a mass is transmitting the pulsations, the ultrasound examination may reveal the origin of the mass and its internal structure. A mass overlying the aorta may obscure the anterior wall of the aorta on the transverse scan, presumably due to the similarity in tissue density.[8] Routine roentgenographic work-up for abdominal masses may then be necessary, which may include aortography and selective visceral angiography to define the nature of the mass. In patients with aneurysms in whom surgery is contraindicated, ultrasonography is an excellent way to follow the patient for change in aneurysm size.

There are potential errors if the ultrasonographic study is not thorough. Both a longitudinal and transverse scan must be done so that the maximum diameter of the aneurysm can be accurately determined. These scans must then be evaluated to ascertain that the aorta is not extremely tortuous. This may result in an overestima-

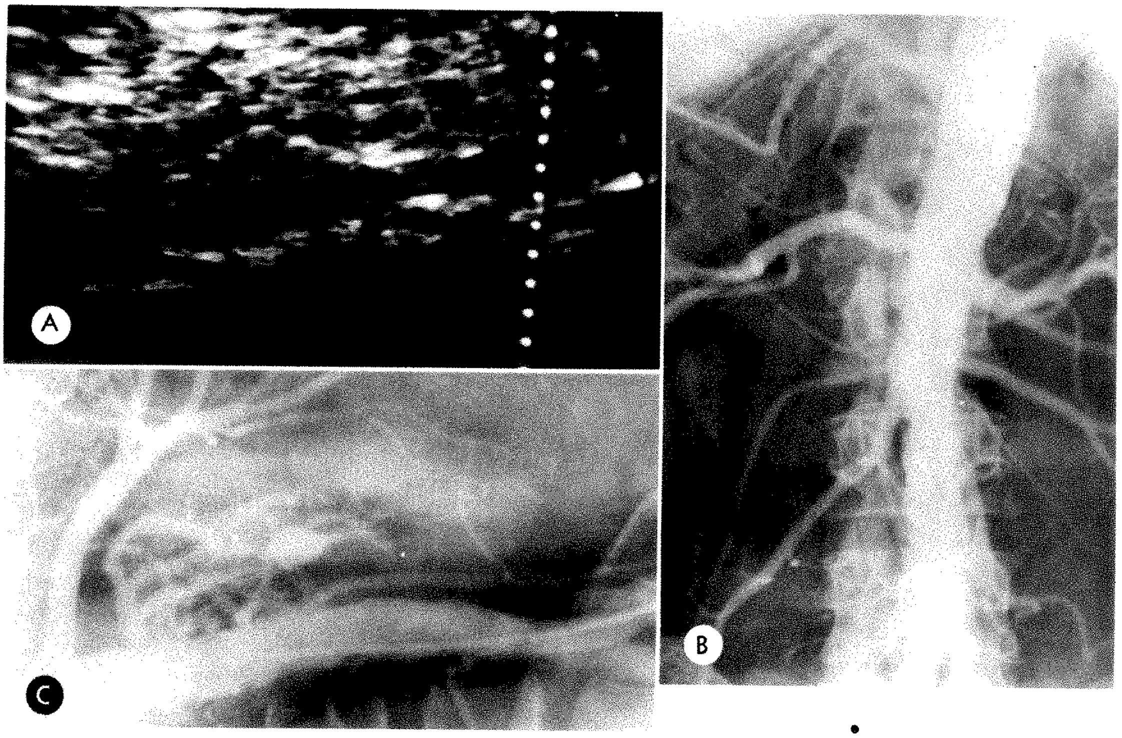

Fig. 4. (*A*) Lateral sonogram on a patient with prominent aortic pulsation demonstrates a normal aortic size and excludes an aneurysm. (*B* and *C*) Anteroposterior and lateral aortograms show a normal aorta.

tion in the size of the aneurysm because the scan has been done obliquely relative to the axis of the aneurysm.[7] Oblique scanning of the patient along the longitudinal axis of the aneurysm and at right angles to this axis will then provide a true measure of the diameter of the aneurysm.

Our study has confirmed other reports of the accuracy of ultrasonic scanning of abdominal aneurysms. There will be patients who will require aortography for suspected renal artery stenosis or ischemia of the mesenteric circulation or of the lower extremities. This information cannot be obtained by any method other than aortography and may be of surgical importance at the time of aneurysmectomy. The vast majority of patients, however, will no longer require aortography if a definitive diagnosis can be established by ultrasonography.

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COARCTATION OF THE AORTA*

ROENTGENOGRAPHIC ASSESSMENT AFTER OPERATIVE CORRECTION

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ABSTRACT:

Persistent abnormalities in the cardiac silhouette and aortic arch are frequent in the late follow-up of patients operated upon for coarctation of the aorta. These abnormalities for the most part can be correlated with age at operation, the presence of a coexistent uncorrected congenital anomaly, or a persistent hemodynamic defect. This group of patients requires continuing clinical and roentgenologic assessment, as these abnormalities are frequently the hallmarks of additional significant cardiovascular disease despite correction of the primary congenital defect.

ALTHOUGH the preoperative roentgenographic features of coarctation of the aorta have been well documented,[2–4,6,11,12,17] detailed findings after coarctation repair have received less attention. The data previously presented usually consist of case reports or findings in selected age groups.[7,9,10,13,22] This study, therefore, was directed toward determining the roentgenographic findings after coarctation repair in one series of patients followed over a period of time. Of particular interest were the correlations between pre- and postoperative abnormal findings, between new roentgenographic changes and hemodynamic status, and the possible reasons for failure of preoperative abnormalities to regress.

MATERIAL AND METHOD

The 190 patients over the age of two years who had coarctation of the aorta resected at the University of Michigan Medical Center between 1957 and 1972 constituted the clinical material. Of these, 105 had recent, high quality, postoperative chest roentgenograms available for evaluation. Ten patients were one to two years postoperative, 46 between three and five years, 32 between six and ten years postoperative, and 17 cases were followed for 11 years or more. All films were specifically evaluated for rib notching, abnormalities of the aortic arch and ascending aortic contour, over-all heart size, specific residual chamber enlargement, and other changes. Correlation was made with physical findings, electrocardiograms, and interim major cardiovascular events, as well as with preoperative and, in some, postoperative catheterization findings. A detailed review of the current cardiovascular status of this material has been recently summarized.[21] In 95 cases the postoperative roentgenogram could be compared with a high quality study taken immediately preoperatively.

RESULTS

Rib Notching. Only 27/72 (37 percent) of those under age 15 at operation had rib notching preoperatively, but 18/23 (78 percent) over age 15 had this finding ($p<.001$) (Table I). No patient with residual coarctation developed *de novo* rib notching. Rib notching persisted in 17 of 45 (38 percent) who had it preoperatively (Fig. 1; Table II). In no patient over the age of 30 at the time of operation did rib notching disappear entirely.

Over-all Heart Size. Preoperatively 78/95 (82 percent) had a normal heart size or only minimal cardiac enlargement, while postoperatively 88/95 (93 percent) had a normal heart size or only minimal enlarge-

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TABLE I

SPECIFIC PREOPERATIVE ROENTGENOGRAPHIC FINDINGS CORRELATED WITH AGE AT OPERATION

	Age at Operation						
	3–15 yr. n=72	Percent	6–30 yr. n=17	Percent	31–60 yr. n=6	Percent	Total n=95
Left Ventricular Hypertrophy							
None	15	21	3	18	—		18
Mild	7	10	5	30	—		12
Moderate	15	21	2	12	—		17
Severe	35	49	7	41	6	100	48
Over-all Heart Enlargement							
None	34	47	10	59	1	17	45
Mild	27	38	4	24	2	34	33
Moderate	10	14	2	12	1	17	13
Severe	1	1	1	6	2	34	4
Rib Notching							
None	45	63	5	29	—		50
Present	27	37	12	71	6	100	45

ment. In 29 patients the heart size returned toward normal; however, four patients had an increase in heart size during the follow-up period (Table III).

Eight patients had residual hypertension postoperatively; of these, three demonstrated some degree of cardiomegaly, while five had a normal sized heart. Nine patients postoperatively had residual coarctation and four of the nine had some degree of cardiomegaly. Thirty patients had aortic insufficiency; eleven of these (37 percent) had some degree of persistent cardiomegaly (Table IV).

Ascending Aorta. In 40 of the 95 patients in the preoperative series, the ascending aorta was normal and remained so postoperatively (Fig. 1). Three patients developed distinct prominence of the ascending aorta at the postoperative examination.

TABLE II

SPECIFIC POSTOPERATIVE ROENTGENOGRAPHIC FINDINGS CORRELATED WITH AGE AT OPERATION

	Age at Operation						
	3–15 yr. n=76	Percent	16–30 yr. n=23	Percent	31–60 yr. n=6	Percent	Total 105
Left Ventricular Hypertrophy							
None	37	49	8	35	—	—	45
Mild	21	28	4	17	1	17	26
Moderate	8	10	1	4	1	17	10
Severe	10	13	10	43	4	67	24
Over-all Heart Enlargement							
None	61	80	12	52	2	33	75
Mild	14	18	7	30	2	33	23
Moderate	—	—	2	9	—	—	2
Severe	1	1	2	9	2	33	5
Rib Notching							
None	74	97	10	43	0	0	84
Present	2	3	13	57	6	100	21

In 52 patients (55 percent) it was prominent on the preoperative examination. In 25 of these patients it was normal at follow-up, while in 27 (52 percent) it remained prominent. Of the 30 patients who have prominence of the ascending aorta postoperatively, seven have aortic stenosis, eleven aortic insufficiency, seven have a bicuspid valve without aortic stenosis or aortic insufficiency, and five a tri-leaflet deformed aortic valve.

Aortic Knob and Descending Aortic Contour. At preoperative examination 54 of 72 (75 percent) patients under age 15 had an abnormal aortic contour, while 13 of 23 (57 percent) over age 15 were abnormal (p = not significant). Twenty-seven patients had a normal appearing aortic knob preoperatively and it remained so postoperatively. One other patient had a normal appearing aortic knob preoperatively, but it appeared abnormal at follow-up. Therefore, in 67 patients the aortic contour was abnormal (large, small or deformed) preoperatively. In 38 of these cases (57 percent) at follow-up it appeared normal on plain chest roentgenography, while in 29 cases the abnormal contour persisted. There was no significant correlation between aortic contour changes and age at operation or associated anomalies.

Left Ventricular Hypertrophy. Preoperatively there was no difference in the prevalence of moderate or marked left ventricular hypertrophy between the younger and older patients. Fifty of 72 patients (69 per-

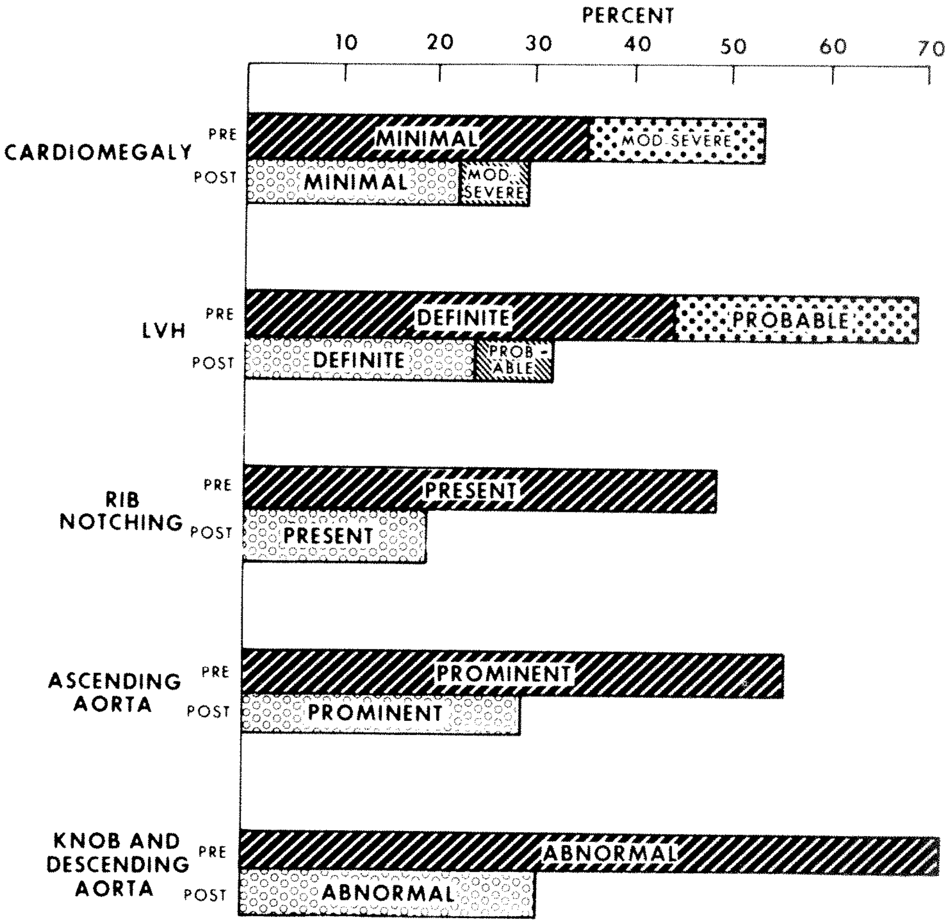

Fig. 1. Summary of preoperative (PRE) and most recent postoperative (POST) roentgenographic abnormalities in the population described.

TABLE III

CORRELATION OF OVER-ALL HEART SIZE PREOPERATIVELY AND POSTOPERATIVELY

Preoperative Over-all Heart Enlargement	Postoperative Over-all Heart Enlargement				
	None	Slightly Enlarged	Moderately Enlarged	Severely Enlarged	Total
Not Available	5	5			10
None	42	2	—	1	45
Slightly Enlarged	22	10	1	—	33
Moderately Enlarged	6	6	1		13
Severely Enlarged	—	—	—	4	4
Total	75	23	2	5	105

cent) in the three to 15 year age group and 15/23 patients (70 percent) over 15 at operation had moderate or severe left ventricular hypertrophy (Table I). Postoperatively, however, only 18 of the 76 patients (24 percent) in the 15 year old and under age group continued to have left ventricular hypertrophy, whereas 16/29 patients (53 percent) over age 15 at operation continued to have moderate or severe left ventricular hypertrophy ($p < .01$) (Table II).

The probable underlying etiology for the persistent roentgenographic evidence of left ventricular hypertrophy is outlined on Table IV. Five of eight patients with persistent postoperative hypertension, six of nine patients with residual coarctation, and 19 of 30 with aortic insufficiency had probable or definite persistent left ventricular hypertrophy. Other hemodynamic abnormalities (subaortic stenosis, mild aortic stenosis, ventricular septal defect, and mitral valvular insufficiency) were also correlated with this persistent roentgenographic abnormality.

DISCUSSION

Successful surgical correction of coarctation of the aorta has been performed for over two decades.[5] Prior studies have emphasized preoperative assessment, improved surgical techniques, and management of immediate postoperative complications.[15,16,20] There have been fewer data available on the clinical long-term follow-up of this group.[8,14,21]

Since the studies of Abbott[1] and Reifen-

TABLE IV

CORRELATION BETWEEN POSTOPERATIVE ROENTGENOGRAPHIC LEFT VENTRICULAR HYPERTROPHY AND COEXISTENT HEMODYNAMIC ABNORMALITIES

	Left Ventricular Hypertrophy						
	None	Percent	Mild or Moderate	Percent	Severe	Percent	Total
Aortic stenosis (congenital and calcific)	2	20	2	20	6	60	10
Aortic insufficiency	11	37	8	27	11	37	30
Hypertension	3	38	3	38	2	25	8
Residual coarctation	3	33	3	33	3	33	9
Ventricular septal defect	1	14	5	71	1	14	7
Mitral insufficiency	2	33	3	50	1	17	6
Subaortic stenosis	4	80	1	20	—	—	5

stein,[18] the frequent occurrence of one or more associated congenital cardiac anomalies in patients with coarctation of the aorta has been appreciated. While anomalies of the aortic valve and patent ductus arteriosus are the most common encountered, numerous other valvular and nonvalvular defects have been described.[19,21]

While preoperative roentgenographic and angiographic changes have received extensive review,[2–4,6,11,12] few data are available concerning the persistence of prior changes or the appearance of new abnormalities on the postoperative chest roentgenogram. This study demonstrates that persistent abnormalities are common and that these abnormalities can be explained in part by coexistent congenital anomalies or by residual hemodynamic defects.

Postoperatively, roentgenographic findings of left ventricular hypertrophy manifested by rounding of the apex and prominence of the heart posteriorly, and abnormalities of the ascending aorta, aortic arch and knob are the most frequently noted signs. The patient's age at operation is one of the major factors influencing the persistence of preoperative roentgenographic signs following operative repair. When the operation is performed under 15 years of age, there is an increased chance that an abnormal chest roentgenogram will revert to normal except for the signs of thoracotomy. Above 15 years of age the abnormal roentgenographic findings are more likely to persist in spite of the correction of the primary defect.

Frederiksen[8] found that only 12.5 percent of those operated upon below age 16 had persistent rib notching, while 50 percent operated upon between 16 and 30 and 68 percent operated upon over age 30 had this finding on follow-up examination. He also emphasized the relationship between age at operation and persistent left ventricular hypertrophy. Twenty-three percent operated upon under age 15, 38 percent between age 16 and 30, and 85 percent over age 30 in the Frederiksen series had left ventricular hypertrophy at follow-up. Very similar results have been demonstrated here.

The prevalence of rib notching in the younger age groups preoperatively has been reported to be as low as two percent under age one[12] and as high as 68 percent between one and seven years.[2] The relationship between rib notching and a significant systolic gradient across the coarctation has recently been emphasized.[2] It is common for rib notching to disappear in the young and remain in adults. Because of the high prevalence of persistent rib notching in adults despite adequate correction of the coarctation, the presence of persistent rib notching was an insensitive hallmark of residual coarctation. This latter persistent defect, however, is most frequently seen in those patients operated upon in childhood.[21]

Not only is age a major determinant of persistent roentgenographic abnormalities, but residual hemodynamic defects (*e.g.*, hypertension and residual coarctation), as well as persistent uncorrected associated congenital anomalies (*e.g.*, aortic stenosis and insufficiency, mitral insufficiency, subaortic stenosis, and ventricular septal defect) also play a significant role in the genesis of the persistent roentgenographic abnormalities. This is outlined in Table IV, which shows that in this series 49 of 61 (80 percent) patients with persistent roentgenographic evidence of left ventricular hypertrophy have a significant hemodynamic lesion. Most of the remaining patients had a period of follow-up of less than three years, and the signs of preoperative left ventricular hypertrophy may not yet have had time to regress. Of note, however, is the low level of sensitivity of the chest roentgenogram in defining these persistent defects. This is in part because of the mildness of most of these defects. No patient with isolated aortic insufficiency, for example, has required valve replacement to date, and only five of the 76 patients in the entire series with any aortic valve involvement have required valvulotomy or valve replacement.[21] A longer period of follow-up is required to determine the natural history of this mild aortic valve involvement in patients with coarctation of the aorta.

These lesions, however, are not of only incidental interest. In this series with a one to 15.5 year follow-up period (mean 6.6 years), there have been 15 deaths. Left ventricular hypertrophy on roentgenography was present in six of the eleven late cardiovascular deaths, and in five of the eleven an associated defect undoubtedly contributed to the patient's demise.

Persistent abnormalities in the contour of the ascending aorta have also been described, and this has been noticed most frequently when coexistent aortic valve disease is present.[7,10] Thirty-nine percent of this material had an abnormal aortic valve by cinearteriography or clinical assessment.[21] Persistent abnormalities in aortic arch contour, however, although not uncommon in the postoperative period, correlated poorly with either age at operation or persistent hemodynamic abnormalities.

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EXTERNAL AND INTERSTITIAL RADIATION THERAPY OF CARCINOMA OF THE ORAL TONGUE*

A REVIEW OF 32 YEARS' EXPERIENCE

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ABSTRACT:

In 204 patients with squamous cell carcinoma of the oral tongue treated with radiation therapy, the most significant prognostic factors appeared to be the presence of neck lymph node metastasis on presentation and the status of the disease three months after treatment. The most common site of failure was the primary lesion, either alone or with neck disease. External irradiation alone was seldom successful. Use of peroral cone irradiation or interstitial implants, either alone or in combination with external irradiation, achieved good local control in early lesions. When the primary tumor was uncontrolled by radiation therapy, salvage with surgery was rare. When failure occurred in the neck alone, radical neck dissection was successful in the majority of cases.

CARCINOMA of the oral tongue accounts for 10 to 15 percent of all head and neck cancers.[5] At the University of California, San Francisco, carcinoma of the oral tongue has been managed primarily with interstitial, peroral or external radiation therapy, or a combination. Surgery has been used to treat persistent or recurrent tumors and cervical lymph node metastases after radiation therapy; it has also been used in combination with radiation therapy to treat advanced lesions and early resectable lesions.

The purpose of this study is to review our experience with radiation therapy in the treatment of carcinoma of the oral tongue and to evaluate the various prognostic factors.

MATERIAL AND METHOD

The records of 204 patients with squamous cell carcinoma of the anterior two-thirds of the tongue treated in the Division of Radiation Oncology, University of California, San Francisco, between 1940 and 1971 were reviewed. Some of the patients were included in previous reports from this institution.[2,12] All of the patients had biopsy-proved moderately to well differentiated squamous cell carcinoma and had a minimum follow-up period of three years. Patients with carcinoma arising from the base of tongue, adenocarcinoma, or other types of malignant tumors of the tongue, and patients who had been referred for treatment of recurrent disease after surgery or radiation therapy elsewhere were excluded from this review. There were 141 males and 63 females. Two-thirds of the patients were between 50 and 70 years of age (Fig. 1).

Based on the clinical descriptions and drawings of the lesions recorded in the patients' charts, the primary lesion and regional lymph node metastasis were retrospectively staged according to the TNM Staging of the American Joint Committee (AJC) for Cancer Staging and End Results Reporting System (Table 1).[6]

Clinical data on these 204 patients were entered into the UCSF Data Retrieval System for computer analysis[13] and were used

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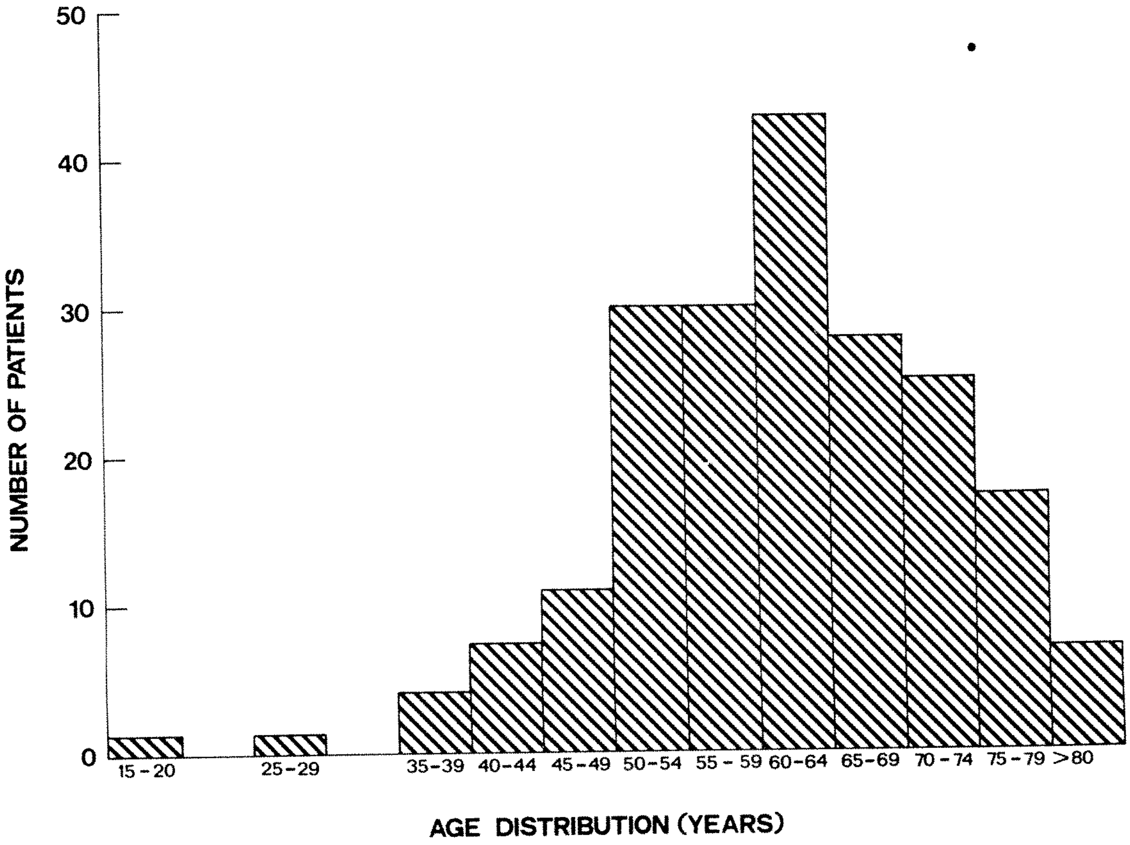

Fig. 1. Age distribution.

to evaluate various prognostic factors, the local control rate, site of failure, and complications of treatment. Survival was calculated with a computerized program based on the method of Bergson and Gage.[3]

TREATMENT

Early lesions were usually treated by interstitial implantation with radium needles or radon seeds either alone or in combination with external irradiation or by peroral cone irradiation. Before 1956 external irradiation was administered with 1 MeV x-rays or orthovoltage equipment. Since 1956 supervoltage equipment, including a 1 MeV GE Maxitron (hvl 3.2 mm Pb), a Theratron F Cobalt 60 (hvl 11 mm Pb), and a 4 MeV linear accelerator, has been used. External irradiation was delivered at 900 to 1,000 rads per week in five fractions in most of the patients. Peroral cone irradiation was administered by a 250 kV GE Maxitron using 100, 200, or 250 kVp with filtration ranging from 2 mm Al to Thoraeus III; the average treatment consisted of 6,000 r in three to four weeks. Surgery was performed in combination with planned preoperative irradiation in eight patients, for local persistence or recurrence, and for cervical lymph node metastasis that developed after radiation therapy for the primary lesion.

RESULTS

Of the 204 patients treated, 43 are alive without disease. One hundred and fifty-eight patients are dead, 44 without tongue cancer (30 died of intercurrent disease, 14 died of second primary cancer), 107 with tongue cancer, and six with disease status unknown. Four patients were lost to follow-up, three without disease and one with disease on last follow-up visit. The crude actuarial survival was 39 percent at three years, 32 percent at five years, and 19 percent at ten years (Fig. 2).

PROGNOSIS

The survival data were analyzed with respect to age, sex, presence of neck lymph node metastasis, stage of disease on presentation, disease status at three months after treatment, and treatment modalities.

Five year survival decreased from 36 percent for patients less than 50 years of age to 30 percent for patients 50 to 69 years of age, and to 22 percent for patients 70 years or older. Although five year survival was greater for females than for males (38 and 29 percent, respectively), the difference was not significant.

On initial examination 46 patients had palpable neck lymph node metastasis and 158 did not. The survival of these 158 patients was significantly higher than that of the 46 patients with lymph node metastases (Fig. 3). Sixty-three of the 158 patients who presented without lymph node metastasis later developed metastases. Their survival was lower than that of the 95 patients who never developed lymph node metastasis (Fig. 3).

According to the AJC staging system, 52 patients had Stage I disease, 82 had Stage II disease, 45 had Stage III disease, and 25 had Stage IV disease on presentation. Survival decreased with each stage, although in our patients the difference in survival between Stage I and Stage II patients was not significant (Fig. 2).

At three months after treatment, 112 patients appeared free of disease and 92 patients had clinically persistent or recurrent disease. The survival of the former group was significantly higher than that of the latter group (Fig. 4).

With respect to treatment modality, the highest survival occurred in patients treated with interstitial implants or with peroral cone irradiation alone. Patients treated with external irradiation alone had the lowest survival (Fig. 5).

Table I

CLASSIFICATION OF CARCINOMA OF THE ORAL TONGUE

American Joint Committee for Cancer Staging and End Results Reporting System	
T.—Primary Tumor	
T1s.	Carcinoma *in situ*
T1.	Tumor ≤ 2 cm in greatest diameter
T2.	Tumor >2 cm but ≤ 4 cm in greatest diameter
T3.	Tumor >4 cm in greatest diameter
N.—Regional Lymph Nodes	
N0.	No clinically palpable cervical lymph node(s); or palpable node(s), but metastasis not suspected
N1.	Clinically palpable homolateral cervical lymph node(s) that are not fixed; metastasis suspected
N2.	Clinically palpable contralateral or bilateral cervical lymph node(s) that are not fixed; metastasis suspected
N3.	Clinically palpable lymph node(s) that are fixed; metastasis suspected
M.—Distant Metastases	
M0.	No distant metastases
M1.	Clinical and/or roentgenographic evidence of metastasis other than to cervical lymph nodes
Staging	
Stage I	—T1 N0 M0
Stage II	—T2 N0 M0
Stage III	—T3 N0 M0 T1 N1 M0 T2 N1 M0 T3 N1 M0
Stage IV	—T1 N2 M0 T1 N3 M0 T2 N2 M0 T2 N3 M0 T3 N2 M0 T3 N3 M0 or any T or N category with M1

LOCAL CONTROL

The over-all control rate of the primary lesion after initial treatment was 50 percent (101/204). The local control rate with radium or radon implants alone was 76 percent (34/45), with peroral cone irradiation alone it was 72 percent (23/32), with external irradiation and interstitial implant

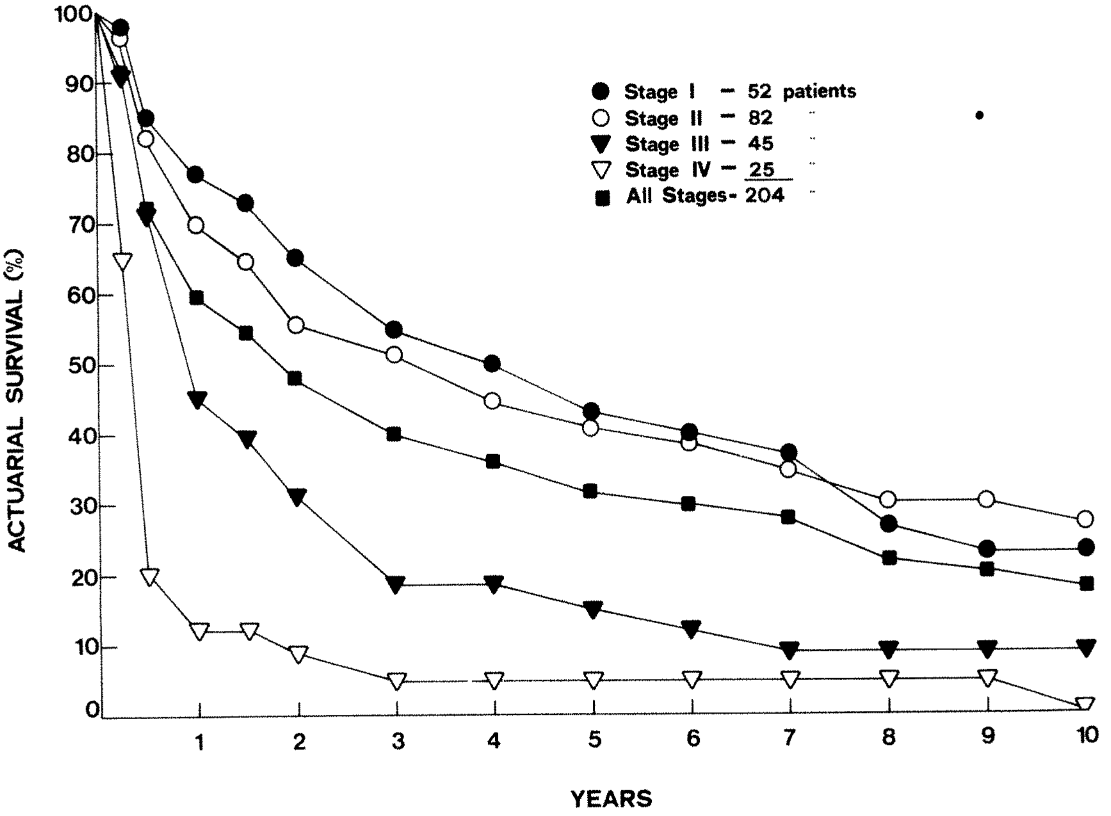

FIG. 2. Survival *versus* stage of disease.

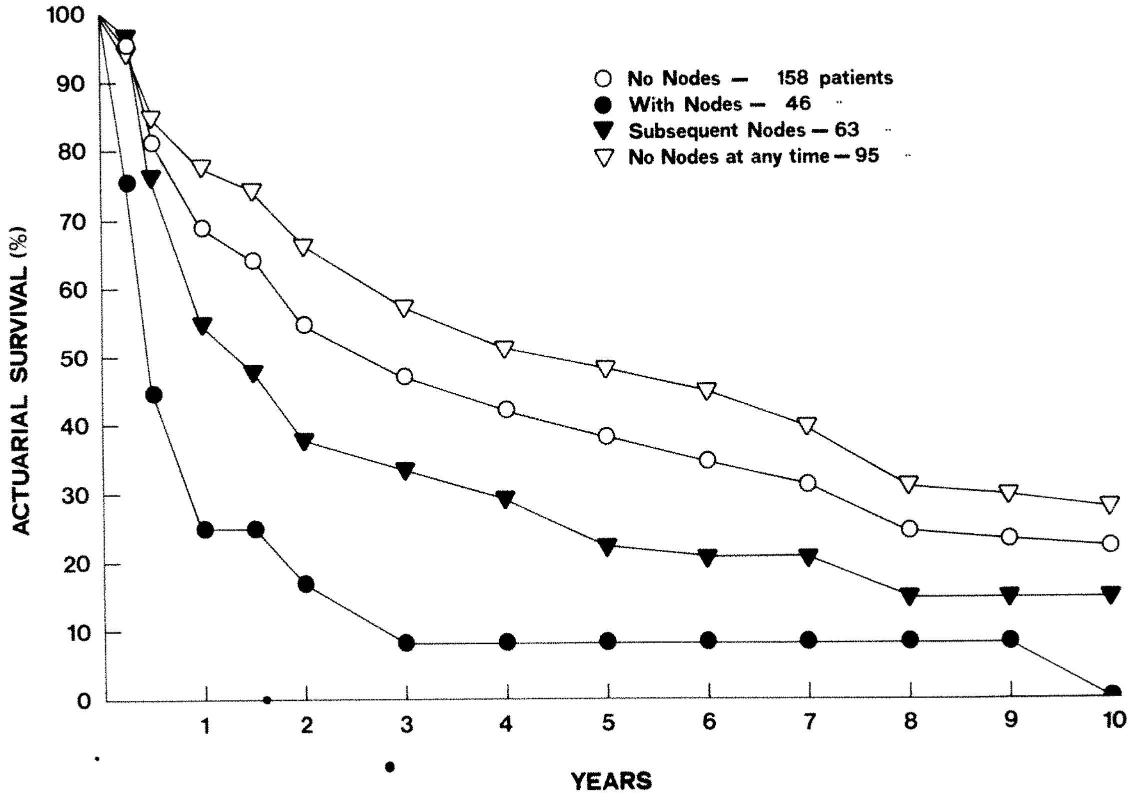

FIG. 3. Survival *versus* status of cervical lymph node metastasis.

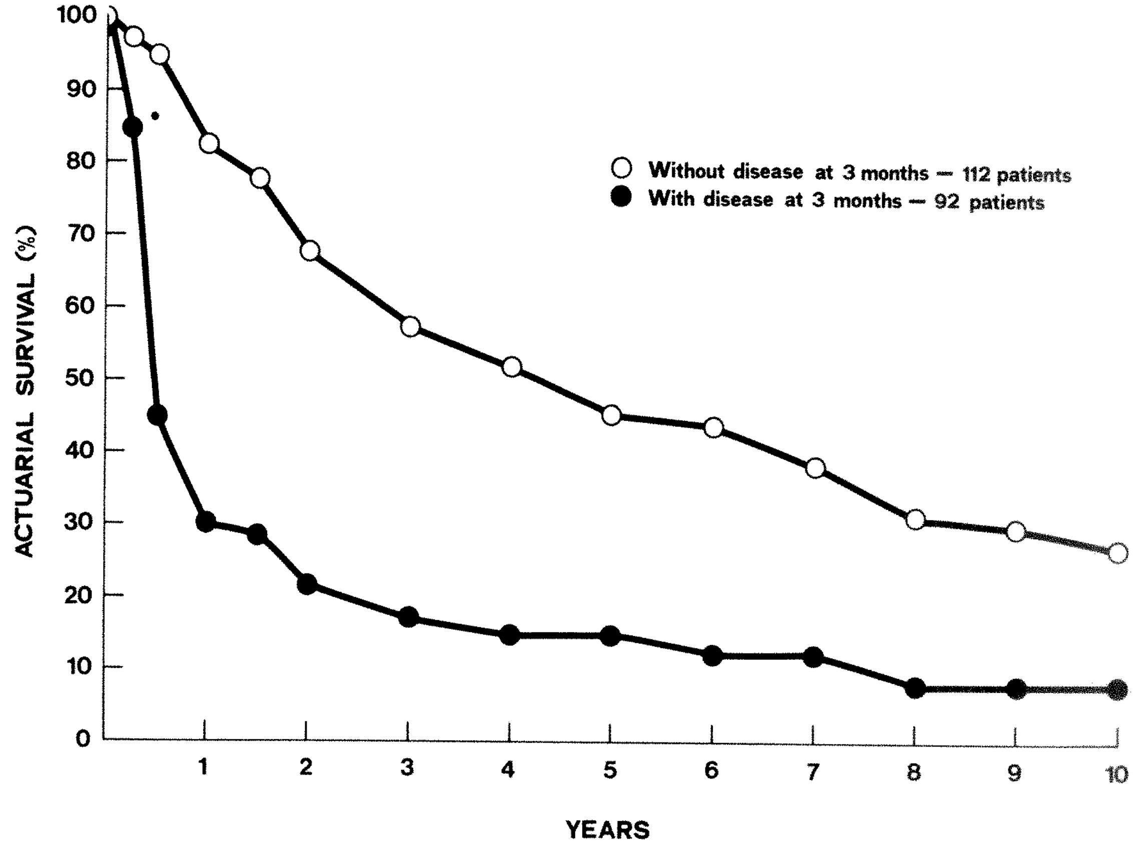

Fig. 4. Survival *versus* disease status at three months after initial treatment.

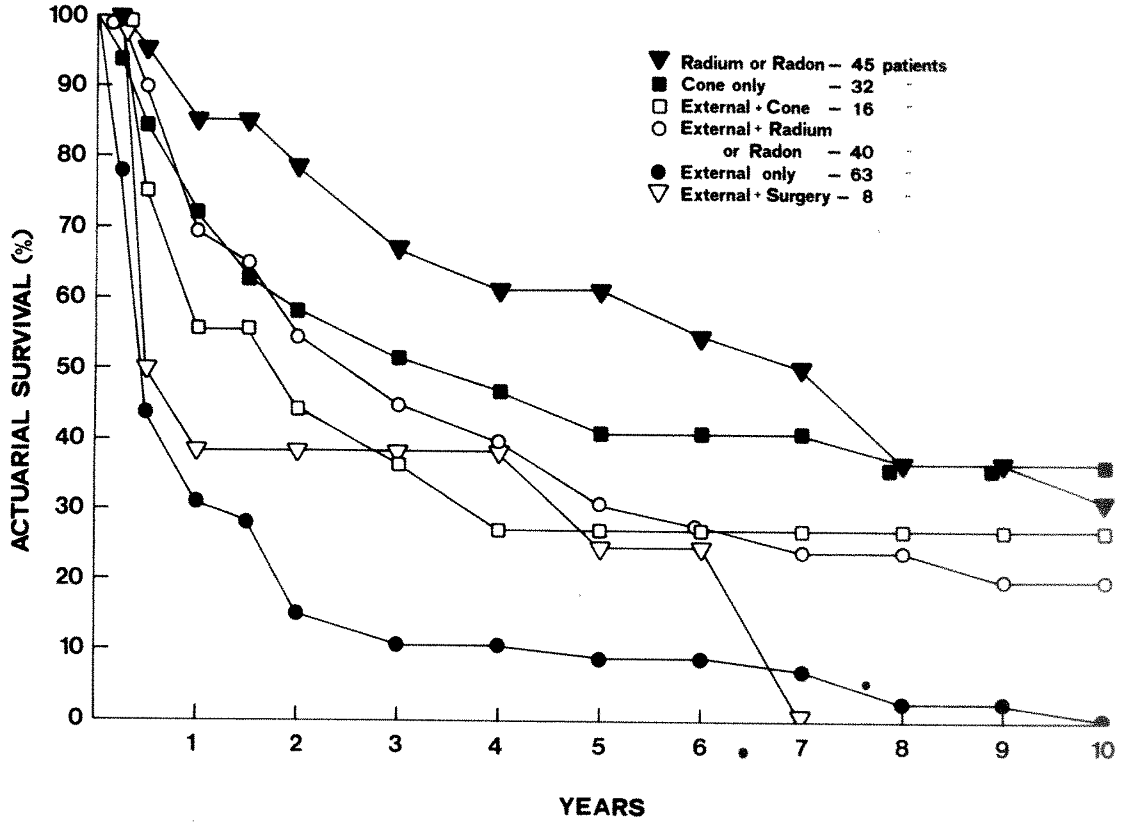

Fig. 5. Survival *versus* treatment modality.

TABLE II

FAILURE OF CONTROL OF PRIMARY AND/OR NECK DISEASE BY STAGE AND TREATMENT MODALITY IN PATIENTS WITHOUT INITIAL NECK DISEASE

Treatment Modality	No. of Patients	Stage					
		T_1		T_2		T_3	
		No.	Percent	No.	Percent	No.	Percent
External only	29	1/3	33	13/16	81	10/10	100
External+peroral cone	13	3/5	60	4/8	50		
External+radium or radon	37	1/6	17	11/22	50	7/9	78
External+surgery	6			2/4	50	1/2	50
Radium or radon	43	9/20	45	11/20	55	3/3	100
Peroral cone only	30	9/17	53	5/13	38		
Total	158	23/51	45	46/83	55	21/24	88

63 percent (25/40), with external irradiation and surgery 50 percent (4/8), with external irradiation and peroral cone 44 percent (7/16), and with external irradiation alone only 13 percent (8/63).

SITE OF FAILURE

In the majority of the patients who presented without neck disease, the most common site of failure after initial treatment, whether the primary lesion was controlled or uncontrolled, was the neck (Fig. 6). The incidence and the site of failure varied with the extent of the primary lesion and treatment modality (Table II). There was a high incidence of failure in the primary in patients treated with external irradiation only. Only 24 percent of the 63 patients treated with external irradiation received more than 6,500 rads, delivered at 900 rads in five fractions per week. In patients treated with interstitial implants alone, failure in the neck was almost twice as frequent as failure in the primary site. In patients treated with interstitial implants or peroral cone irradiation in combination with external irradiation, failure in the primary site was as frequent as failure in the neck.

Of the 58 patients who failed in the primary site, only seven were salvaged by surgery, retreatment with radiation therapy, or both. After salvage, the most common ultimate site of failure was the primary, either alone or with neck disease (Fig. 6).

Most of the patients with neck lymph node metastasis when first seen had more advanced primary lesions and were treated with external irradiation only. They failed in the primary as well as in the neck (Fig. 7). Twenty-five (twelve percent) of the entire group of patients developed distant metastasis, most frequently in the lung, bones, or liver.

Cervical Lymph Node Metastasis. In the 46 patients (23 percent) who had neck lymph node metastasis on presentation, neck disease was controlled with external irradiation in six and with radical neck dissection in two.

Of the 158 patients who did not have palpable cervical lymph nodes initially, neck lymph node metastasis subsequently appeared in 63 patients (40 percent); thirty of these had uncontrolled primaries. Ninety percent of the subsequent neck lymph node metastases appeared within 18 months after treatment. Cervical lymph node metastasis developed after treatment in only 29 percent of the T1 lesions and in 32 percent of the T2 lesions, but in 92 percent of the T3 lesions. Previous partial neck irradiation did not seem to alter this incidence, even at doses greater than 5,000 rads (Table III). However, the radiation fields

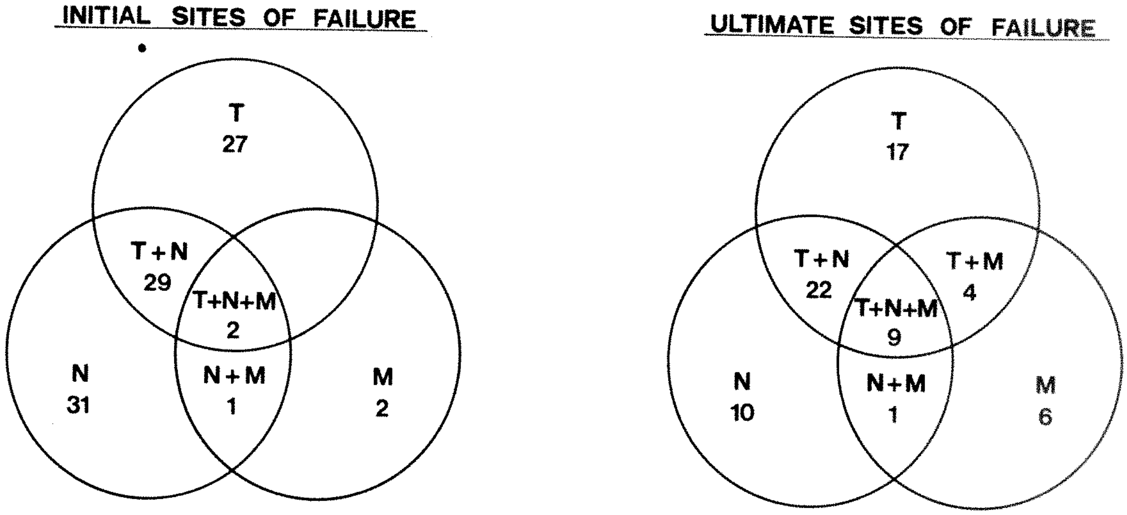

Fig. 6. Sites of failure in patients without neck lymph nodes on presentation. T=primary site; N=neck lymph nodes; M=distant metastases.

were inadequate to cover retropharyngeal lymph nodes and upper cervical lymph nodes, and the primary was uncontrolled in most of these patients.

No further treatment was given to 21 of the 63 patients with subsequent neck disease. Of the remaining 42 patients, subsequent neck disease was controlled in 19 of the 24 patients (79 percent) treated with radical neck dissection and in two of the five patients (40 percent) treated with radical neck dissection in combination with external irradiation. Neck disease was uncontrolled in the eight patients who underwent resection of the primary in conjunction with neck dissection, in the two patients treated with radiation therapy in addition to surgical resection of the primary and the neck disease, and in the three patients treated with radiation therapy alone.

COMPLICATIONS

Thirty patients developed soft tissue necrosis, six patients developed bone ne-

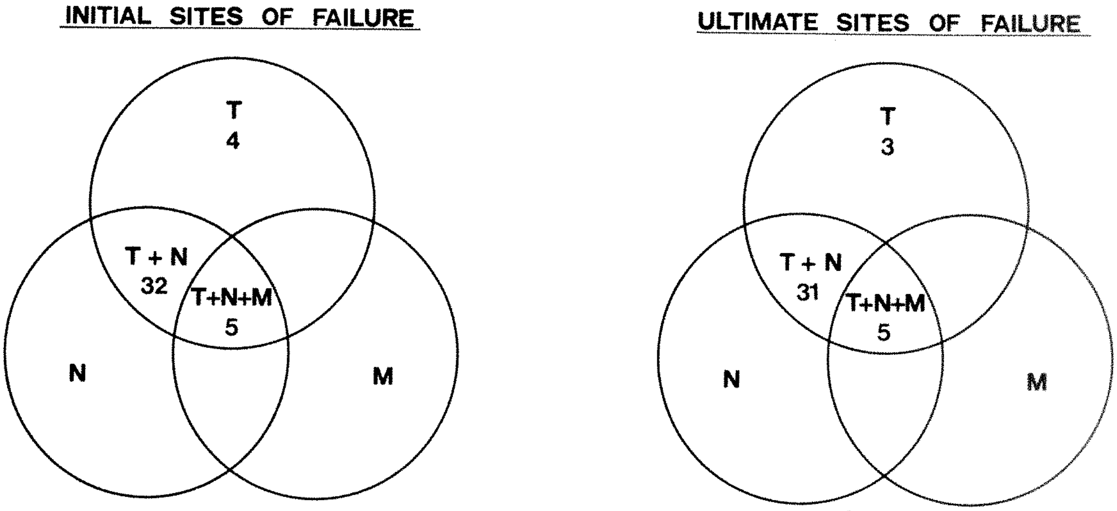

Fig. 7. Sites of failure in patients with neck lymph nodes on presentation. T=primary site; N=neck lymph nodes; M=distant metastases.

TABLE III

INCIDENCE OF SUBSEQUENT NECK LYMPH NODE METASTASES IN PATIENTS WITHOUT INITIAL NECK DISEASE *vs.* PREVIOUS NECK IRRADIATION

Treatment of Initially Negative Neck		Incidence of Subsequent Neck Disease	
		No.	Percent
No irradiation		30/73	41
Partial neck irradiation	≥5000 rads	19*/51	37
	<5000 rads	14†/34	41
Total		63/158	40

* 15 had uncontrolled primary disease, 10 developed lymph nodes outside the irradiated neck.
† 5 had uncontrolled primary disease, 8 developed lymph nodes outside the irradiated neck.

crosis, and two patients had necrosis of both the soft tissues and the bone. The time of appearance of necrosis varied from two months to six years after treatment, although 76 percent of the necroses appeared within two years. The majority of the soft tissue necroses healed with conservative management; only one patient was treated with limited resection. Four patients underwent partial mandibulectomy for radionecrosis of the bone. Thus, the incidence of severe complications requiring surgical intervention was only 2.4 percent.

SECOND PRIMARY

Thirty-nine (19 percent) of the patients had second cancers in other primary sites (Table IV) and eight patients had more than one second primary. Most of the second primary sites were in the upper respiratory or alimentary tracts. It is interesting that a clearly separate site in the tongue was the most common second primary site.

DISCUSSION

Our results are in general agreement with other reported series of carcinoma of the tongue treated with radiation therapy.[1,4,7,11,14] Although local control was achieved ultimately in 53 percent of the patients, five year actuarial survival based on the Bergson and Gage[3] method was only 32 percent. This survival rate was not corrected for deaths from intercurrent disease in 30 patients and deaths from a second primary cancer in 14 patients who died without evidence of disease in the tongue.

The most significant prognostic factor was the presence or absence of cervical lymph node metastasis. In patients with neck lymph nodes on presentation, the five year survival rate was eight percent, in contrast to 48 percent in patients who never developed neck lymph node metastasis. This is consistent with the experience of other investigators.[4,7–9,11,14] When there

TABLE IV

NUMBER OF PATIENTS WITH SECOND PRIMARY CANCER: 39*/204 (19 PERCENT)

Site of Second Primary	No. of Patients
Tongue	7
Larynx	6
Lung	5
Soft palate	5
Alveolar ridge	5
Esophagus	3
Tonsil	3
Pyriform sinus	2
Floor of mouth	2
Maxillary sinus	1
Lip	1
Skin	2
Colon	2
Bladder	2
Stomach	1
Pancreas	1
Hepatoma	1
Melanosarcoma	1
Breast	1

* 8 patients had more than one second primary.

was persistent or recurrent disease three months post-treatment, the prognosis was also very poor.

Survival also varied with treatment modality. The primary lesion was rarely controlled with external irradiation alone, regardless of size. This is not surprising since most of the patients treated with external irradiation alone had advanced disease, and the radiation dosage, which was below 6,500 rads given in six and one-half to seven and one-half weeks, was probably too low. Interstitial implants with either radium needles or radon seeds and peroral cone irradiation were successful in the initial control of primary lesions in 76 and 72 percent of the cases, respectively. However, most of these patients had relatively early lesions.

Control of subsequent neck disease appeared to be related to the status of the primary lesion at the time the neck disease was detected. When the primary was uncontrolled and combined resection was required, the disease was not controlled. When the primary lesion was controlled, the neck disease was controlled in 79 percent of the patients who underwent radical neck dissection.

Our complication rate is similar to that reported by Montana *et al.*[11] Although 38 patients (18.6 percent) developed soft tissue, or bone necrosis, or both, severe complications requiring surgery occurred in only five patients (2.4 percent). There were 74 patients treated with interstitial radium implants alone or in combination with external irradiation. Localization films or diagrammatic reproductions of the implant geometry were found for 58 of them. Retrospective computer analysis of the isodose distribution of the implants in these patients revealed that the incidence of necrosis correlated well with sizable volumes of overdosage; details of this analysis will be reported in a separate communication.[10]

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COMPARISON OF SPLIT-COURSE RADIATION THERAPY AND CONTINUOUS RADIATION THERAPY FOR UNRESECTABLE BRONCHOGENIC CARCINOMA: 5 YEAR RESULTS*

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ABSTRACT:

One hundred and eighty-eight patients with inoperable or unresectable bronchogenic carcinoma were stratified by cell type, TNM staging, and prior surgery and then randomized into two treatment groups: continuous radiation therapy and split-course radiation therapy. There was no difference in clinical or objective improvement in the two groups. Survival rates for cases of squamous cell carcinoma, small cell carcinoma, and adenocarcinoma were the same after both regimens of therapy. Split-course therapy resulted in a significantly better survival rate in cases of large cell carcinoma but the number of cases was small. We doubt that the difference is clinically significant.

Objective roentgenographic response was accompanied by improved survival in squamous cell carcinoma, but not in the other three cell types.

Split-course radiation therapy is superior to continuous radiation therapy because it is better tolerated by the patient and because re-examination of the patient prior to the second half of split-course therapy permits the detection of new metastatic disease that has become manifest during the rest period and spares the patient the futile second half of radiation therapy.

SCANLON[22] first advocated split-course radiation therapy in 1959. Despite 15 years of research, however, the exact radiobiologic mechanism remains unknown. Sambrook[20] has stated that "the really crucial theoretic argument in favor of the split-course principle rests on the consideration of cell population kinetics." Basically, cell damage by ionizing radiation strongly stimulates reparative proliferation, but the differential is great between normal cells and malignant cells. Tumor cells respond to this stimulus much more slowly—a characteristic that can be exploited in split-course radiation therapy. Another concept is that reduction in tumor size by the first course may result in improved vascularization within the tumor and reoxygenation of hypoxic tumor cells, rendering them more susceptible to destruction by the second course of radiation therapy.[20,21,23,24] Electrodes implanted into human tumors have demonstrated that oxygen tension rises dramatically in previously hypoxic regions after completion of a course of irradiation.[20]

Logically, then, a rest interval between two courses of irradiation should render the tumor more susceptible to destruction by the second course. And, theoretically, the process of alternating irradiation and rest could be continued indefinitely, until all tumor cells were destroyed, were not the total dose limited by tolerance limits of the healthy surrounding tissues.[20]

Radiation therapy is of definite but

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From the Mayo Clinic and Mayo Foundation, Rochester, Minnesota.
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limited value in the treatment of bronchogenic carcinoma.[2,5,9,11,12,14,17,25] Often it fails because of persistence of cancer in the area that is treated. But, in addition, most patients with bronchogenic carcinoma that cannot be resected have distant metastases that are not detectable by even careful pretreatment evaluation. This has led to the search for a systemic agent that might be given along with radiation therapy to control the occult metastasis, to increase the effectiveness of the irradiation within the field of treatment, and to increase the quality and duration of the survival of the patient.

In 1964, the Mayo Clinic Lung Cancer Study Group began a series of clinical trials to study radiation therapy combined with a number of chemotherapeutic agents. The chemotherapeutic aspects of this study were emphasized in a previous report.[6] For years radiation therapists have argued the merits of split-course *versus* continuous radiation therapy for patients with unresectable bronchogenic carcinoma.

This report gives the five year results of the first of these clinical trials and compares split-course and continuous radiation therapy in patients with inoperable and unresectable bronchogenic carcinoma.

MATERIAL AND METHOD

All patients with inoperable or unresectable bronchogenic carcinoma referred for treatment were admitted to the study if they satisfied the following criteria:

1. Clinical and roentgenographic evidence and histologic or cytologic proof of bronchogenic carcinoma.
2. No previous therapy for the cancer other than palliative resection.
3. Demonstrable cancer involving no more than the affected lung, mediastinum, and ipsilateral supraclavicular space, without pleural effusion, and acceptable to the radiation therapist for a total midplane dose of 5,000 r.
4. Absence of life-threatening concomitant disease.
5. General condition and blood counts adequate for intensive therapy.
6. Consent to remain in Rochester for treatment and return for follow-up examinations after thorough explanation of the investigational nature of the plan of treatment.

Because the various cell types of bronchogenic carcinoma are so different in prognosis and clinical characteristics, we classified our cases into the four groups (according to cell types) currently used at the Mayo Clinic (squamous cell carcinoma, small cell carcinoma, adenocarcinoma, and large cell carcinoma). Classification of each case was verified by one of two particular members of the Department of Surgical Pathology. The extent of each patient's cancer was staged by a system developed from the principles of the American Joint Committee on Cancer Staging and End Results Reporting.[8] Because the use of exploratory thoracotomy and palliative resection was believed important prognostically, groups were created according to the presence of any prior surgery. Consequently the patients were stratified by prior surgery and stage within each cell type. The regimen of therapy was then selected at random by use of a sealed envelope system.

A total midplane dose of 5,000 r (4,700 rads) was given by the split-course or continuous method of radiation therapy, using photons from a 6.3 MeV linear accelerator with a half-value layer of 16 mm of lead. The target skin distance was 100 cm or the target axis distance, 100 cm. No correction was made for tissue inhomogeneity. Anterior and corresponding posterior portals were arranged to include the primary tumor, the mediastinal lymph nodes, and the ipsilateral supraclavicular region if these lymph nodes were abnormal.

For the split-course radiation therapy, a daily midplane dose of 175 to 200 r, five or six days per week, was given for 12 to 14 days. After a rest period of three to four weeks, the patient was re-evaluated, and, if no contraindication was found, a second similar course was given to bring the total midplane dose to 5,000 r over a period of seven to nine weeks. For the continuous radiation therapy, a daily midplane dose of 175 to 200 r, five or six days per week, was given to a total of 5,000 r over a period of four to five weeks.

We evaluated the split-course and the continuous methods of radiation therapy with and without 5-fluorouracil (5-FU) as an adjuvant. The 5-FU, in a dose of 10 mg/kg of body weight (using the smaller of the ideal or the actual body weight) per day, was given by rapid intravenous injection for the first five days of the radiation therapy. Each portion of the split-course radiation therapy was accompanied by a course of 5-FU at its onset. Chemotherapy was discontinued if serious toxicity occurred (*e.g.*, stomatitis, vomiting, diarrhea, leukopenia, or thrombocytopenia).

The results of treatment were evaluated primarily by the use of survival rates. In addition, objective changes in the roentgenograms were measured, and changes in the patient's symptoms and general condition were recorded. Additional treatment for recurrence of the cancer or distant metastasis was given as needed, in addition to supportive therapy such as transfusions, antibiotics, and analgesics.

After completion of therapy, each patient was asked to return regularly for re-evaluation. Through this re-evaluation or correspondence with his personal physician, we evaluated each patient's clinical condition three months after completion of treatment. To be considered improved, the patient had to have fewer symptoms and be more active than at the beginning of treatment. Of course some patients could not improve; they were asymptomatic or had few symptoms at the beginning of treatment. Roentgenographic change was determined by comparison of the pretreatment chest roentgenogram with the one showing maximal improvement that was obtained during either the period of therapy or the following three months. To be classified as an objective response, the best roentgenogram had to show complete clearing of obstructive pneumonitis secondary to the tumor or at least a 50 percent decrease in the size of the tumor (sum of the perpendicular diameters).

By the time accrual was stopped on March 31, 1968, the study included 188 patients. All patients have been followed until death or for a minimum of five years.

RESULTS

The survival rates for each of the five years after beginning continuous or split-course radiation therapy are shown in Figure 1. There was no significant difference for squamous cell carcinoma, small cell carcinoma, or adenocarcinoma. For the large cell undifferentiated carcinoma, however, the results after split-course radiation therapy were significantly better than the results after continuous radiation therapy. The results were not significantly improved by the addition of 5-FU.

Quality of life may be almost as important as survival. The treatment was of benefit to a significant number of the patients, but no single regimen of therapy was superior to the others. Each of the regimens of therapy was equally effective in producing roentgenographic improvement (Table I). Small cell cancer was more responsive than the other cell types. Addition of 5-FU was not associated with more frequent roentgenographic changes or with improved quality of life.

Analysis of our groups revealed no unusual distribution among the regimens of age,[3,16] sex,[7] symptoms,[10] and site of the primary tumor,[4] which have been reported to affect the prognosis. Of the 188 patients, 56 percent were clinically inoperable, 25 percent had thoracotomy without resection, three percent had thoracotomy with partial resection, and 16 percent had no thoracotomy for medical reasons or because of refusal by patient. Table II shows the completeness of therapy for each cell type. The most common cause of failure to complete the planned therapy was the development of distant metastasis. This was

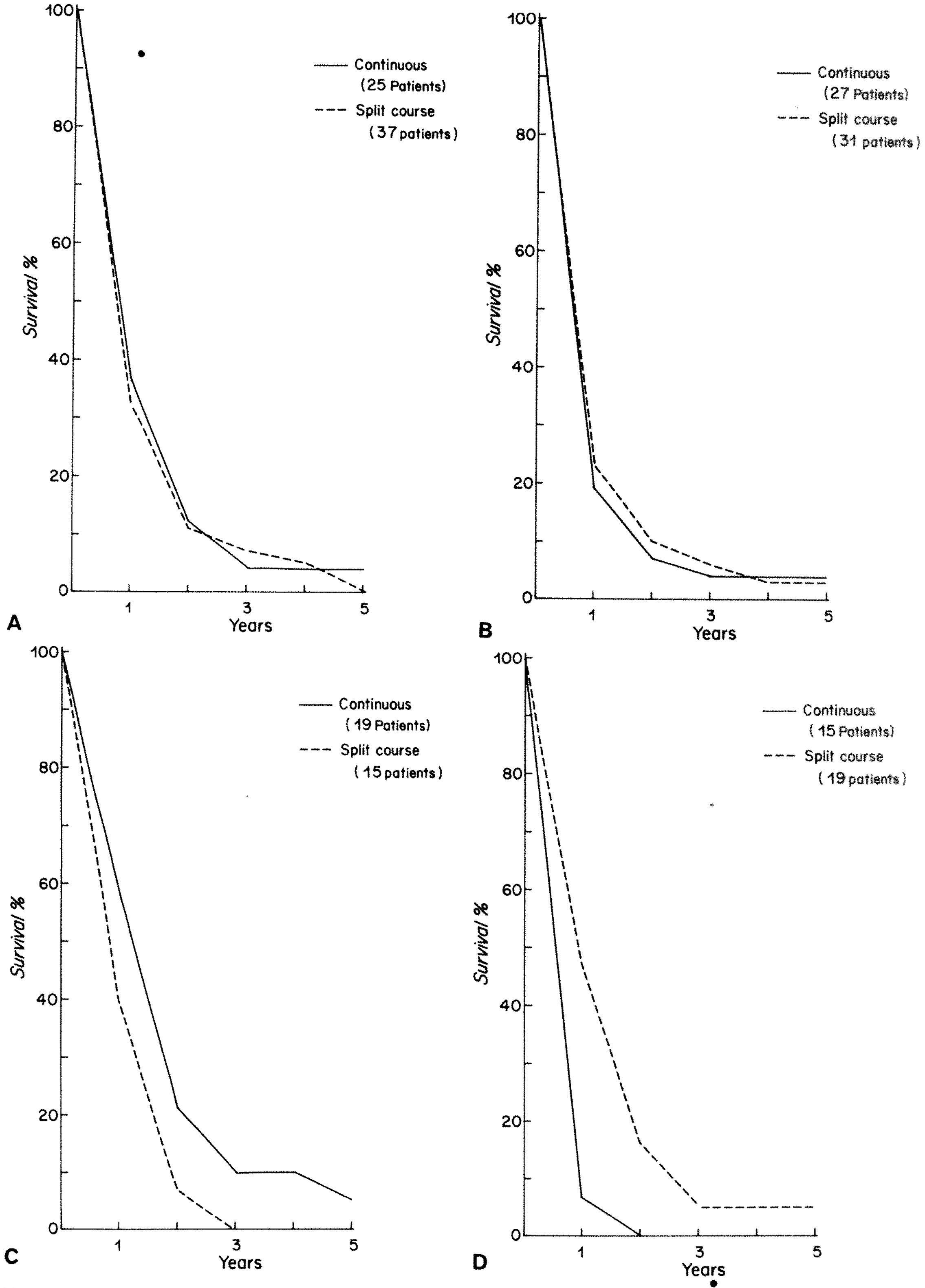

FIG. 1. Survival by year for patients with various cell types of bronchogenic carcinoma treated with split-course radiation therapy or continuous radiation therapy. (*A*) Squamous cell carcinoma (62 patients). (*B*) Small cell carcinoma (58 patients). (*C*) Adenocarcinoma (34 patients). (*D*) Large cell carcinoma (34 patients).

TABLE I

ROENTGENOGRAPHIC CHANGES AFTER TREATMENT

Lesion	Radiation			
	Continuous		Split-course	
	No. of Patients*	Percent Objective Response	No. of Patients†	Percent Objective Response
Squamous cell carcinoma	25	32	37	46
Small cell carcinoma	27	78	31	71
Adenocarcinoma	19	42	15	53
Large cell carcinoma	15	47	19	37
Total	86	51	102	53

* Follow-up data unavailable in 9 of these patients.
† Follow-up data unavailable in 11 of these patients.

more frequent for split-course therapy and for small cell carcinoma, as the four week interval between the two courses of treatment was long enough for occult metastases to become clinically obvious. Toxic reaction to 5-FU was the second most common cause of incomplete therapy, requiring omission of the second course of chemotherapy.

COMPLICATIONS

The complication rates were similar following split-course radiation therapy and continuous radiation therapy. In almost all the patients who lived three months or longer following therapy, radiation pneumonitis became apparent roentgenographically within three to six months. This gradually developed into radiation fibrosis which was present at one year in virtually all patients. Symptoms due to radiation pneumonitis and fibrosis were uncommon.

Because the portals encompassed mediastinal lymph nodes, about half of the patients developed transient esophagitis. The dysphagia usually started after two weeks of radiation therapy, persisted for a few days to two weeks, and then subsided spontaneously.

Radiation pericarditis and radiation myelitis were not diagnosed in these patients, possibly because two-thirds of the patients died within one year after treatment. (Radiation pericarditis may occur six months to eight years after exposure,[19] and radiation myelitis usually requires a year or more to develop.[18])

TABLE II

COMPLETENESS OF THERAPY (PERCENT) IN UNRESECTABLE BRONCHOGENIC CARCINOMA ACCORDING TO CELL TYPE AND REGIMEN OF THERAPY

Therapy	Squamous Cell	Small Cell	Adenocarcinoma	Large Cell
Continuous radiation				
4,500–5,000 r	88	85	95	93
<4,500 r	12	15	5	7
Split-course radiation				
4,500–5,000 r	92	68	87	94
<4,500 r	8	32	13	6

DISCUSSION

Our survival rates were similar for the four cell types using either continuous radiation therapy or split-course radiation therapy. Our data are in agreement with the reports of Holsti[13] and Levitt *et al.*[15] who found no significant difference in survival rates or in symptomatic relief between the two regimens of therapy.

In contrast, Abramson and Cavanaugh[1] reported a better survival rate for patients treated with split-course radiation therapy than those treated with continuous radiation therapy. However, this study was not a randomized clinical trial. The split-course radiation therapy consisted of 2,000 rads in five days, followed by a three week rest period and then a second course of 2,000 rads in five days. These authors[2] have extended their study of the short split-course technique to a series of 347 patients and have reported a five year survival rate of six percent (five of 85 patients at risk). For the patients, this short two week course has great practical and economic advantages compared to the usual course requiring five to six weeks. We are now participating in a randomized clinical trial to compare this ten treatment, 4,000 rad split-course technique with our standard 25 treatment, 5,000 rad split-course technique.

Comparison of survival times of the patients who had complete clearing or marked roentgenographic improvement with the rest of the patients revealed no differences in survival for those with small cell carcinomas, adenocarcinomas, or large cell carcinomas. However, patients with squamous cell carcinoma who had complete clearing or marked roentgenographic improvement had longer survival times than the rest of the patients with this cell type ($P=0.01$). This may be due to the tendency of squamous cell bronchogenic carcinoma to spread through the lymphatic system to the regional lymph nodes rather than by hematogeneous dissemination. Consequently, more of the patients with squamous cell carcinoma may have had disease limited to the thorax, and, if so, there might be a significant relationship between radiation-induced regression of the tumor and survival. Because the other cell types tend to invade the blood vessels and develop metastases earlier in the development of the primary tumor, the effect of the radiation therapy on the tumor might have less relationship to the survival of patients with tumors of these cell types.

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Vol. 126, No. 1

MEDIASTINAL HODGKIN'S DISEASE*

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ABSTRACT:

A group of five patients with Hodgkin's disease, nodular sclerosing in type, localized to the mediastinum (Stage IA) is reported. We believe that this presentation, sometimes known as "granulomatous thymoma," warrants management in a manner somewhat different from that of the more common presentations of Hodgkin's disease. Nodular sclerosing Hodgkin's disease involving only the mediastinum affects a younger age group in whom the disease may be asymptomatic. Making the diagnosis may necessitate a thoracotomy, but an attempt should be made to obtain tissue short of thoracotomy, as by mediastinoscopy. An extensive attempt at surgical extirpation is not necessary because the disease is very radiosensitive and radiocurable. The combination of Stage I Hodgkin's disease, nodular sclerosing in form, limited to the mediastinum favors an excellent prognosis.

WHILE Hodgkin's disease frequently involves the mediastinum, it is uncommonly the sole site of involvement. When the mediastinum is the sole site of involvement, the nodular sclerosing type is the usual form, and the thymus is frequently involved. Radiation therapy is the treatment of choice and extensive staging procedures may be unnecessary.

In one large series, 211 of 340 consecutive untreated patients with Hodgkin's disease of all stages presented with mediastinal involvement; in five, the mediastinum was the sole site of involvement.[8] In another large series of 203 patients (Stages I, II, and III), the mediastinum was involved in 110, solely in six.[17] In a comparison of four series of patients other than our own with Stage I Hodgkin's disease, mediastinal involvement only occurred in six of 56,[8] five of 56,[6] six of 53,[17] seven of 107[7] and thus a total of 24 of 272 patients (8.8 percent) (Table I). This report is presented as a review of an experience with this entity and with recommendations regarding its management.

Table I

MEDIASTINAL INVOLVEMENT IN FIVE SERIES OF PATIENTS WITH STAGE I HODGKIN'S DISEASE

Ibrahim *et al.*[7]	1972	7/107
Kaplan[8]	1972	6/56
Hutchinson[6]	1972	5/56
Smithers[17]	1973	6/53
Vaeth	1975	5/18

MATERIAL

A series of 55 consecutive, previously untreated Hodgkin's disease patients, all stages, was irradiated by the authors from July, 1965 to October, 1970. Sixteen of these patients presented initially with mediastinal involvement; the disease in five was only in the mediastinum, in eleven there was supraclavicular or supraclavicular and axillary lymphadenopathy as well. Of 18 Stage I patients, five had only mediastinal involvement (Table II). Of the other 13 patients with single site involvement, the regions were: supraclavicular and cervical, nine; axilla, two; inguino-femoral, one; retroperitoneum, one.

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TABLE II

COMPARISON OF SITE OF MEDIASTINAL INVOLVEMENT TO TOTAL CASES: HODGKIN'S DISEASE (1965–1970)

Total Stages I, II, III	55
With mediastinal involvement initially	16
Total Stage I Patients	18
With mediastinal involvement	5

Of these five patients with only mediastinal involvement, three were females and two were males. The ages varied from 19 years to 48 years (mean age, 33.2 years). There were 24 females and 26 males in the remaining 50 cases of this series (the mean age of the remaining 50 cases was 36.3 years).

CLINICAL FINDINGS

Three of the five patients were asymptomatic when a routine chest roentgenogram revealed the anterior mediastinal mass. One other patient had severe substernal pain of less than 24 hours' duration leading to the diagnostic chest roentgenogram. Another patient had dyspnea, more on exertion, and anterior pleuritic-type pain of six weeks' duration, before her diagnostic roentgenogram examination was performed and an anterior mediastinal mass noted. In all, the mass as observed on the roentgenogram was considered to be limited to the mid upper anterior mediastinum without hilar or paratracheal lymphadenopathy. None had cough or hemoptysis. None had vena caval compression signs. Three of the five were cigarette smokers.

In four of the five patients, the histological diagnosis of Hodgkin's disease was made at thoracotomy. While the surgeons reported that the majority of the tumor was removed in these four cases, adjacent lymph nodes and pleura were involved and the dissection was incomplete. (In one of these four, the tumor was dissected off the pericardium.) The diagnosis of anterior mediastinal Hodgkin's disease was made in the fifth patient by mediastinoscopy and biopsy, thus averting an exploratory thoracotomy.

HISTOLOGY

The histology of all five mediastinal cases was nodular sclerosing Hodgkin's disease. This histologic type of Hodgkin's disease enjoys a reputation of carrying a more favorable prognosis, especially in early stages.[1,2,12,14,16,18] In 13 of the 15 cases with mediastinal involvement, the histology was nodular sclerosing Hodgkin's disease. We do not regard nodular sclerosing Hodgkin's disease of the thymus as a separate pathological entity, *i.e.*, granulomatous thymoma. Indeed, the two entities are considered to be one and the same.[3,4,9,10,13,15,16]

Of the 55 cases, 22 were nodular sclerosing, of whom 13 had mediastinal involvement, five as the sole site. There were also four lymphocytic predominant, 25 of mixed cellularity, and three with lymphocytic depletion. Of the 18 Stage I cases (16, IA; and 2, IB) nine were nodular sclerosing, six of mixed cellularity, and three were lymphocytic predominant. The comparison of histology in the entire series and those with mediastinal involvement is shown in Table III.

Of the 107 Stage I Hodgkin's disease cases reported by the M. D. Anderson group, 38 were nodular sclerosis, involving only the mediastinum in seven.[7]

TABLE III

HISTOLOGY AND RELATIONSHIP TO MEDIASTINAL INVOLVEMENT (1965–1970)

	Entire Series	Mediastinum	
		Total	Only
Lymphocyte predominance	5	—	—
Nodular sclerosis	22	13	5
Mixed cellularity	25	2	—
Lymphocyte depletion	3	—	—

TREATMENT AND SIDE EFFECTS

All five cases received Cobalt 60 teletherapy, utilizing an anterior mediastinal-bilateral infra-supraclavicular field (which encompassed the apex of the axilla) and a posterior mediastinal field. Both fields, anterior and posterior, were treated daily in three of the patients, alternate fields daily in the other two patients. Irradiation was conducted four times weekly with a mid week and weekend rest. Mid plane mediastinal doses varied from 4,500 rads/23 fractions/40 days to 4,950 rads/32 fractions/49 days. In all, treatment was well tolerated with a transient esophagitis being the dominant side effect.

In none are there late side effects; specifically, there was no pericarditis, myelitis or subcutaneous fibrosis. All show post irradiation paramediastinal lung fibrosis on follow-up chest roentgenogram; in none is this symptomatic or debilitating.

RESULTS

Of the 15 cases with mediastinal involvement, two have recurred in the mediastinum (one with widespread disease; the other with a marginal recurrence which was re-irradiated). Two other patients (who are alive five years after initial mediastinal irradiation) had recurrence below the diaphragm and were re-irradiated. They are free of disease one and one-half and six years after re-irradiation.

None of the five patients with only mediastinal disease has demonstrated progression of disease into adjacent or distant lymph node areas; none has progressed to systemic disease. Their survivals vary from four and one-half years to nine and one-half years. One of these five patients had a local recurrence at the medial margin of a left lung block and is considered to represent a marginal underdose, four and one-half years after mediastinal irradiation. She was explored by thoracotomy, the recurrence was documented and localized, and she was further re-staged by abdominal laparotomy and bone marrow biopsy. The chest was found to be the only site of recurrence. She was re-irradiated to the local left thoracic recurrence. If the mediastinal field marginal recurrence is the only site of recurrence in initially limited disease, the prognosis remains good.[19]

DISCUSSION

Bone marrow biopsy and lymphangiography are desirable to assist in accurately staging the disease. Pulmonary function testing should be performed prior to a lymphangiogram. Chest tomography should be performed to further document the extent of thoracic involvement with disease. A surgical laparotomy with nodal biopsies, splenectomy, and liver biopsy is not necessary.

The treatment of choice is radiation therapy, even if the tumor may seem to have been excised at thoracotomy. The treatment volume need encompass only the mass, the mediastinum, hilar regions and the infra- and supraclavicular regions, bilaterally. We have found that delivery of 800–900 rads per week, irradiating both anterior and posterior fields four times weekly, is well tolerated. Although the cases described received total doses in excess of 4,000 rads, these higher dose levels may not be necessary. Experience has shown that in many instances there may be incomplete roentgenographic evidence of clearance of the mediastinal disease at 4,000 rads, but that this is not indicative of residual neoplasm.

The prognosis with radiation therapy is excellent if the mediastinum is the initial site of presentation.[5,7,11,16,18] It is even better if it is the sole site of involvement.

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ELECTIVE IRRADIATION WITH THE ELECTRON BEAM AFTER MASTECTOMY FOR BREAST CANCER*

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ABSTRACT:

From 1963 to 1970, 380 patients have received elective treatment with the electron beam after radical mastectomy for breast cancer. One hundred and twenty-nine patients received treatment to the supraclavicular and internal mammary lymph node areas only, and 251 patients received treatment to the chest wall as well as to the areas of peripheral lymphatic drainage. Analysis of the results shows the value of elective irradiation of occult deposits of disease since the incidence of local recurrences is significantly less than would be anticipated in this group of patients.

THE electron beam is preferred for the irradiation of the areas of peripheral lymphatic drainage and the chest wall after radical mastectomy because of the ease of treatment and the minimal lung irradiation. The supraclavicular lymph nodes are located just under the skin and could be undertreated, unless build-up material is used, during irradiation with the 4 to 6 MeV photon beam. Treatment of the internal mammary lymph node chain with the megavoltage photon beam gives a high dose to the mediastinal structures, including the hilar vessels, pericardium, and myocardium. With the electron beam the energy is selected for the depth of minimum tumor dose, with rapid fall-off in dose beyond this point.

Treatment of the chest wall with tangential photon fields is more complex and there is significant dosage to the lungs. At M. D. Anderson Hospital, with few exceptions, the electron beam is always used to treat the chest wall along with the peripheral lymph nodes. Because the time available on the electron beam is limited, when the chest wall does not require treatment, the peripheral lymph nodes may be treated with ^{60}Co, since it provides a satisfactory dose distribution.

CLINICAL INDICATIONS FOR TREATMENT PLANNING

The extent of the initial disease correlated with local control and recurrence patterns influences the selection of the plan of treatment. The histologic status of the axillary lymph nodes in the operative specimen correlates closely with the incidence of disease in both the supraclavicular and internal mammary lymph node areas. Robbins *et al.*,[9] reporting on two series of patients with breast cancer treated at Memorial Hospital, found an incidence of 26 per cent metastasis to supraclavicular lymph nodes in 200 patients who had positive axillary lymph nodes at operation and who did not receive postoperative radiation therapy. Jackson[8] reported a similar incidence of disease developing in the supraclavicular area when the axillary lymph nodes were positive in the surgical specimen. The location of the tumor in the breast and the degree of involvement of the

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axillary lymph nodes have been definitely correlated with the incidence of metastasis in the internal mammary chain of lymph nodes.[1,3,7,11,12]

The incidence of recurrence of breast carcinoma in the chest wall after radical mastectomy is clearly correlated with the percentage of involved axillary lymph nodes. Dao and Kovaric[4] noted a chest wall recurrence rate of 27 percent in patients with more than 15 positive axillary lymph nodes in the operative specimen. In Spratt's series[10] of 704 patients with breast carcinoma treated by radical mastectomy, chest wall recurrences were seen in 40 to 45 percent of patients with heavily invaded axillary lymph nodes. Chu *et al.*[2] describe a 23 percent recurrence rate in the chest wall in patients with positive axillary lymph nodes treated by radical mastectomy alone. Haagensen[6] reported chest wall recurrences in 35 to 40 percent of 17 Stage A and 33 Stage B patients with eight or more positive axillary lymph nodes.

In patients treated at the M. D. Anderson Hospital by radical mastectomy followed by irradiation of the peripheral lymphatic drainage areas only, the chest wall recurrence rate was 4.5 percent when the axillary lymph nodes were negative, 11 percent with less than 50 percent positive lymph nodes and 22 percent with more than 50 percent positive lymph nodes.

TECHNIQUE

PERIPHERAL LYMPH NODE IRRADIATION

If there is no evidence of extranodal disease in the axillary specimen, even if many positive lymph nodes were recovered, only the apex of the axilla requires treatment to dovetail with the surgical procedure. With incomplete dissection of the axilla or with extranodal disease, or both, the entire axilla requires treatment with ^{60}Co, utilizing both anterior and posterior axillary portals.

After radical mastectomy, the treatment fields used to irradiate the adjacent lymphatic drainage areas include the ipsilateral supraclavicular lymph nodes, the apex of the axilla, and the internal mammary lymph node chain (Fig. 1). The supraclavicular field is treated with 11 MeV, which gives 90 percent of the dose at 2.5–3 cm. The given dose is 5,000 rads in four weeks, 250 rads daily. The dose to the lymph nodes is at least 4,500 rads. The internal mammary field is treated with 15 MeV, which gives 90 percent of the dose at 4 cm and receives the same given dose as the supraclavicular field. In the very low-risk patients, *i.e.*, those with small outer or inner quadrant lesions and only one or two positive lymph nodes low in the axilla, the given dose is 4,500 rads, which provides

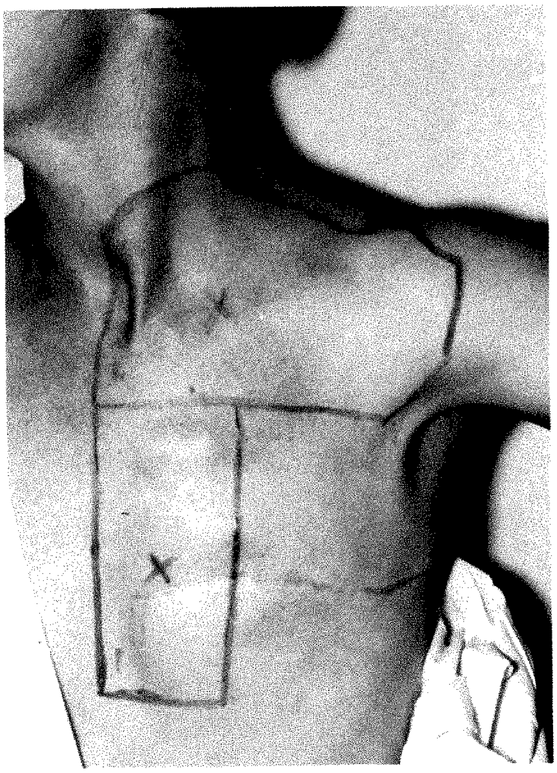

FIG. 1. The supraclavicular field extends from the midneck down to the lower border of the sternal end of the first rib and the head of the clavicle, covering the supraclavicular fossa and subclavicular apex. The internal mammary field is positioned 1 cm across the midline on the contralateral side and measures 7 cm in width. The inferior margin is placed at the xyphoid-sternal junction, and the entire ipsilateral internal mammary lymph node chain is included in the field.

4,000 rads tumor dose in three and one-half weeks to the supraclavicular and internal mammary lymph nodes. If the axillary lymph nodes are negative with a small central or inner quadrant lesion, only the first three intercostal spaces are treated to a given dose of 4,500 rads in three and one-half weeks (Fig. 2).

CHEST WALL IRRADIATION

The average chest wall thickness after radical mastectomy is 1.5 to 2.0 cm, a depth well covered by the 90 percent dose range of 7 MeV. When the chest wall thickness approaches 3 cm, then 9 MeV is used. The chest wall portal must include the full extent of the mastectomy scar; if the scar cannot be satisfactorily covered by one field, small contiguous fields are added. If the mastectomy scar extends across the sternum, this portion of the scar may be included in the 15 MeV internal mammary field (Fig. 3, *A* and *B*) or is treated by a separate small 7 MeV field.

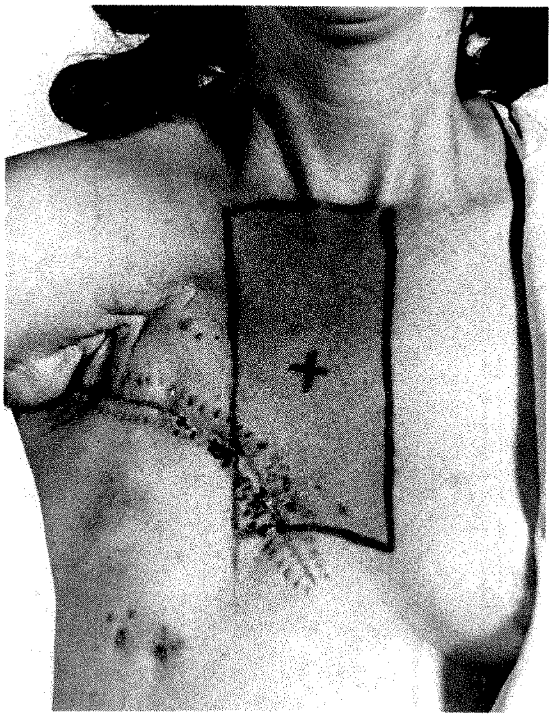

Fig. 2. This patient had a 1.5 cm upper inner quadrant breast carcinoma. The axillary lymph nodes recovered at radical mastectomy were negative. The treatment field covers the first, second, and third internal mammary lymph nodes. Treatment is given with 15 MeV, 4,500 rads given dose in three and one-half weeks.

The chest wall field adjoins the internal mammary and supraclavicular fields and extends laterally to the midaxillary line. The lateral portion of the field is treated with beam fall-off over the curve of the rib cage. This results in a lower dose to the lateral chest wall than the dose to the mid-chest wall where the source-skin distance is measured. If the difference in dose is significant or if the patient's scar extends transversely across the chest wall and into the axillary line, a lateral oblique electron beam portal is added (Fig. 3, *A* and *B*).

The dose to the large anterior chest wall field is 5,500 rads given dose in four weeks. The dose to the lateral oblique field has been reduced to 5,000 rads given dose in four weeks because of the intensity of the skin reaction with the tangential beam.

RESULTS OF ELECTIVE TREATMENT

PERIPHERAL LYMPHATICS

From May, 1963 through December, 1970, the electron beam has been used in 129 patients to treat the peripheral lymphatic drainage areas after radical mastectomy. Eleven of the 129 patients had more than 50 percent positive axillary lymph nodes but did not receive chest wall treatment because of delayed healing of the chest wall. The results are shown in Table I. Only one patient developed a supraclavicular lymph node recurrence as well as a chest wall recurrence. No patient developed a parasternal nodule. Ten patients had chest wall recurrences, all outside the irradiated area. Seven of these ten patients had lesions located in the central or inner quadrants of the breast, six patients had more than 25 percent positive axillary lymph nodes, and nine patients had grave signs.

PERIPHERAL LYMPHATICS AND CHEST WALL

From May, 1963 through December, 1970, the electron beam has been used in

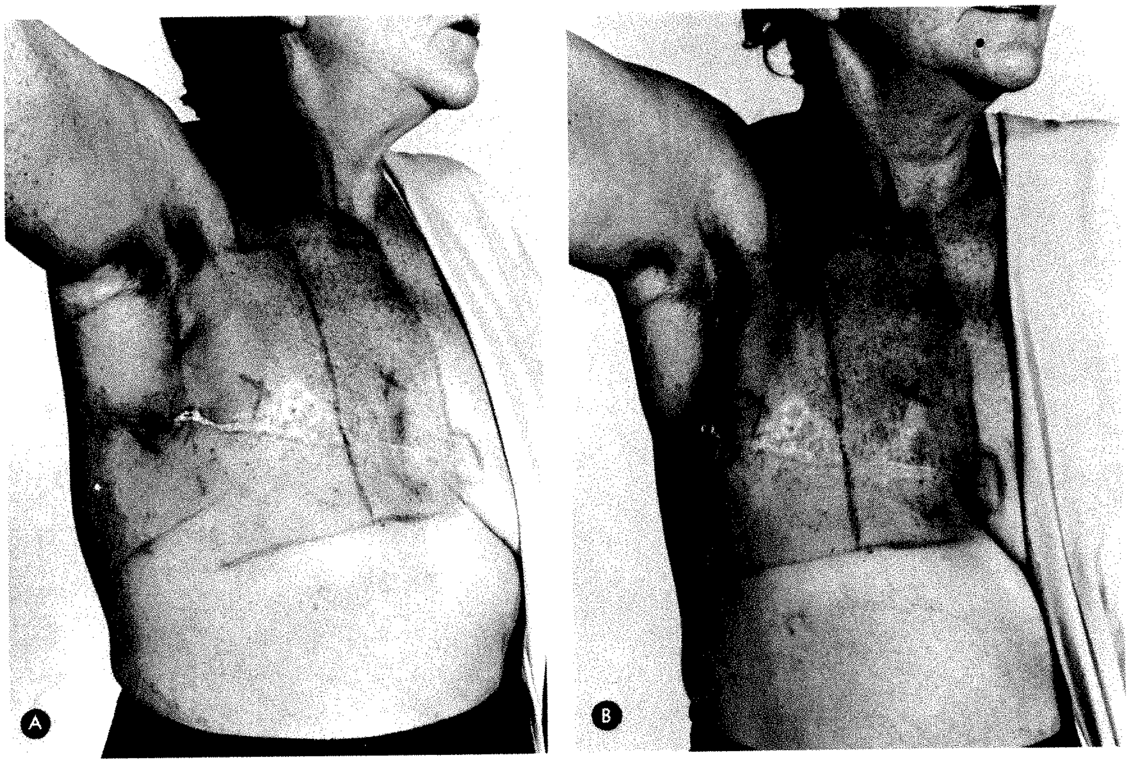

Fig. 3. (*A* and *B*) The mastectomy scar extends transversely across the chest wall from the contralateral breast to the posterior axillary line. The internal mammary field has a lateral projection to include the medial end of the scar. The lateral chest wall and posterior extension of the scar are covered by an oblique chest wall field. The patient is nearing completion of treatment and has developed erythema and dry desquamation. The reaction is more intense in the supraclavicular and internal mammary areas, treated with 11 MeV and 15 MeV, respectively, than the reaction in the chest wall, treated with 7 MeV.

251 patients for treatment of the peripheral lymphatic regions and the chest wall after conventional or modified radical mastectomy. Table II shows the extent of axillary lymph node involvement. Seventy-six percent of the patients had grave signs, 70 percent had more than 25 percent positive axillary lymph nodes, and only ten patients (four percent) had neither grave signs nor a large number of positive axillary lymph nodes. Approximately one-half of the patients had lesions measuring more than 5 cm in diameter.

The results of treatment in the 251 patients are shown in Table III. Recurrence in the chest wall has developed in 31 patients (twelve per cent). In three patients the recurrence was outside the treatment fields

Table I

PERIPHERAL LYMPHATICS IRRADIATION ONLY: RESULTS IN 129 PATIENTS

May 1, 1963 to December 31, 1970
Analysis of March 1974

Alive NED* 3–8 yr.	Supraclavicular Recurrences	Parasternal Nodules	Chest Wall Recurrences	Distant Metastases
87	1	0	10	39

* NED = no evidence of disease.

—one at the posterior axillary line, one below the internal mammary field, and one on the inner aspect of the upper arm. In two patients the recurrence was at the periphery of the fields in the lower and lateral chest wall area where the dose was low, and in three patients disease appeared in the chest wall after extensive carcinoma had appeared in the second breast. Treatment to the chest wall was stopped at a dose of 3,900 rads in one patient because of breakdown of a crusted chest wall wound. In the remaining 22 patients, definite nodules, some biopsy-proved, appeared well within the area of high dose irradiation. Seventy percent of these patients had lesions located in the central or inner quadrants of the breast and 84 percent had 25 percent or more positive axillary lymph nodes. Six patients developed supraclavicular lymph node recurrences, which is an excellent control rate in view of the heavy invasion of the axilla in these patients.

Table II

DISTRIBUTION OF PATIENTS WHO RECEIVED ELECTIVE IRRADIATION OF CHEST WALL AND PERIPHERAL LYMPHATICS: CLINICAL FEATURES OF THE PRIMARY DISEASE AND PERCENTAGE OF INVOLVED AXILLARY LYMPH NODES IN OPERATIVE SPECIMEN

251 Patients
May 1, 1963 to December 31, 1970
Analysis of March 1974

Percent Positive Axillary Lymph Nodes	No Grave Signs*	Grave Signs*
<25 percent 74 patients	10	64
>25 percent 177 patients	51	126

* See Table v.

COMPLICATIONS

Electron beam treatment to the supraclavicular and internal mammary lymph

Table III

RESULTS OF ELECTIVE IRRADIATION OF CHEST WALL AND PERIPHERAL LYMPHATICS CORRELATED WITH PERCENTAGE OF INVOLVED AXILLARY LYMPH NODES IN OPERATIVE SPECIMEN

May 1, 1963 to December 31, 1970
Analysis of March 1974

Total Patients Treated 251	Chest Wall Recurrence 31 Patients		Recurrence in Peripheral Lymphatics‡ or Distant Metastases, or both 131 Patients§	
	<25 Percent Positive Axillary Lymph Nodes	>25 Percent Positive Axillary Lymph Nodes	<25 Percent Positive Axillary Lymph Nodes	>25 Percent Positive Axillary Lymph Nodes
Alive no evidence of disease 102 patients	0	3†	0	0
Alive with disease 22 patients	0	2	7	15
Dead with disease 127 patients	5*	21	25	84

* These 5 patients had grave signs (See Table v).

† 2 patients had recurrences at the lateral edge of the chest wall field at 18 and 22 months; 1 patient had recurrence below the internal mammary field at 6 months. The lesions were excised, the scars were irradiated, and the patients are NED at 40, 28, and 84 months, respectively.

‡ 6 patients developed supraclavicular lymph node recurrences; 5 patients had 35 to 85 percent positive axillary lymph nodes; 1 patient had 20 percent positive lymph nodes.

§ In 131 patients with distant metastases, some patients also had chest wall and supraclavicular lymph node recurrences.

Table IV

INDICATIONS FOR IRRADIATION OF PERIPHERAL LYMPHATIC DRAINAGE AREAS ALONE

Location of Lesion in Breast	Histology Axillary Lymph Nodes	Areas Irradiated
Outer quadrants	Negative	None
Small inner or central quadrants lesion	Negative	Internal mammary chain lymph nodes 1, 2, and 3 interspaces
Outer, inner, or central quadrants No grave signs	Few positive	Areas of peripheral lymphatic drainage*

* Supraclavicular fossa, apex of axilla, internal mammary lymph node chain.

nodes has been without complications of any significance. Initially the given dose was 5,400 rads in three and one-half weeks and the nine or ten patients who developed a small area of asymptomatic subcutaneous fibrosis in the supraclavicular fossa received this dose. A few patients developed telangiectasia. The dose was reduced to 5,000 rads in four weeks in 1968, when a review of the data indicated almost 100 percent local control with 5,000 rads given in four weeks. Occasional mild fibrosis and telangiectasia have been seen in the patients treated with this dose.

Initially, in treatment of the chest wall, the dose given was 6,000 rads in four weeks, 300 rads daily. A small number of patients developed late sequelae of multiple telangiectasia and subcutaneous fibrosis. Because of this, the dose was lowered by 10 percent—to 5,500 rads given in four weeks. The local control rate has remained the same with a decrease in the incidence of telangiectasia and fibrosis.

When large fields are used to treat the chest wall to a given dose of 5,500 rads in four weeks, the skin reaction is usually a brisk erythema with extensive dry desquamation. An occasional patient has exhibited patchy moist desquamation which healed rapidly.

Radiation pneumonitis, usually asymptomatic and seen as pulmonary fibrosis of limited extent in serial roentgenograms, developed in a small number of the patients treated prior to 1966. The extent of pulmonary reaction can be correlated with the energy used in the treatment of the chest wall. The most severe reactions have been produced when the chest wall was treated at 9 MeV. Initially the technique used to treat the chest wall required the patient to be rotated up on the side in order to provide as much flattening of the chest wall as possible to avoid the lateral fall-off in dose. This resulted in crossfiring the parasternal area by the internal mammary field and the chest wall field. With 7 MeV, only rarely has a patient developed symptoms of radiation pneumonitis, and roentgenographic evidence of fibrosis has been minimal.

Chest wall irradiation must not be initiated until there has been complete healing of the mastectomy wound. Healing is not considered satisfactory if there is thick crusting along the mastectomy scar or a fluid collection under the chest wall flaps. If healing is incomplete, chest wall irradiation carries with it considerable potential for chest wall necrosis, and breakdown of the wound may occur during treatment or shortly after it is concluded. With breakdown of the chest wall, spontaneous healing may require four to six months or longer; necrosis with persistent ulceration may develop and require surgical resection and grafting. Of the 251 patients who received treatment to the chest wall as well as to the peripheral lymphatic drainage areas, eleven developed chest wall necrosis which was severe in three patients.

Seven of the eleven patients had shown poor healing after mastectomy and two required secondary grafting. Ten of the eleven patients healed completely in two to 18 months; two patients required excision of the necrosis.

Skin grafts do not present a hazard in irradiation of the chest wall if the graft has taken well. Even very thin grafts which are closely adherent to the rib cage tolerate electron beam doses of 5,500 rads in four weeks and remain in good condition.

PRESENT INDICATIONS FOR ELECTIVE POSTOPERATIVE IRRADIATION

Patients who have a small lesion located in the central or medial portions of the breast and who have no positive axillary lymph nodes could receive irradiation only to the first three internal mammary chain lymph nodes, which is the only lymphatic area at a significant risk of invasion.[1,11] Patients who have few positive axillary lymph nodes recovered at operation and who exhibit no grave signs receive irradiation only to the ipsilateral lymph nodes in the supraclavicular fossa, the apex of the axilla, and the internal mammary chain (Table IV). Irradiation is given to the entire chest wall as well as to the peripheral lymphatics in those patients who have extensive involvement of the axillary lymph nodes in the operative specimen or who exhibit grave signs. With lesions in the central or inner quadrants, one should tend more toward chest wall irradiation, since the incidence of chest wall recurrence is higher than with lesions in the outer quadrants. The indications for treatment of the chest wall after radical mastectomy are listed in Table V.

Table V

INDICATIONS FOR IRRADIATION OF PERIPHERAL LYMPHATIC DRAINAGE AREAS AND CHEST WALL

20 Percent or More Positive Axillary Lymph Nodes	
Grave Signs	1. Breast tumor >5 cm 2. Fixation of tumor to pectoral fascia 3. Skin fixation, edema, or erythema 4. Multiple foci of invasive tumor 5. Vascular, perineural, or lymphatic invasion

In some patients, data as to the location and characteristics of the tumor, the clinical status of the axilla, and sometimes even the pathological specimen, are not clear. One must then tend toward more extensive treatment, being guided by the thickness of the flaps, the presence or absence of the pectoral muscle, and clinical judgment of the quality of the axillary dissection. Chest wall irradiation with 7 MeV (9 MeV in thick chest walls) is essentially free of significant complications and, therefore, is warranted in patients whose initial disease indicates a definite risk of chest wall recurrence.

SUMMARY

The population of patients exposed to a significant risk of recurrent disease in the peripheral lymphatics or the chest wall, or both, has been clearly defined.

Using 11 MeV electrons to treat the supraclavicular and axillary apex lymph nodes and 15 MeV to treat the internal mammary chain lymph nodes, 5,000 rads given in four weeks result in almost 100 percent eradication of disease in the peripheral lymphatic drainage areas. A given dose of 5,500 rads in four weeks with 7 MeV electrons prevents the appearance of chest wall disease in almost 90 percent of the patients.

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VOL. 126, No. 1

TREATMENT SELECTION IN PRIMARY BREAST CANCER*

PATHOLOGIC CONSIDERATIONS

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ABSTRACT:

Minimal breast cancer is defined as including *in situ* lobular carcinoma, noninvasive intraductal carcinoma, and invasive carcinoma forming a mass no greater than 0.5 cm in diameter. Intraductal, intralobular, and microinvasive carcinomas of this degree of development are classed together, and are associated with at most a 10 percent probability of having associated axillary lymph node involvement. Lesions of this classification have been shown to have a five year survival rate of 97 percent and a ten year rate of 95 percent, when they are treated surgically.

BREAST cancer is, both in prevalence and costliness, the single most important neoplasm in the United States today. At the same time it is the most frustrating. Decades of effort have produced only minor reductions in mortality. The greatest obstacle to the achievement of meaningful improvement in breast cancer survival is the conception of carcinoma as a lump in the breast. Such a viewpoint ignores the fundamental nature of this disease and militates against effective utilization of methods of early detection.

Over the past 15 years Dr. John Martin and I have examined more than 200 surgically removed, cancer-containing breasts by combined subserial whole organ sectioning and mammography.[1–3] Although this study was originally designed to elucidate relationships between mammographic changes and their histopathologic counterparts, it has also yielded considerable information about the early phases in the development of mammary carcinoma. It has been found, for example, that hyperplasia of ductal and lobular epithelium is a regular concomitant of invasive carcinoma. Further, it has been demonstrated that there is a continuum of histologic change from simple hyperplasia through hyperplasia with cellular atypism to noninvasive carcinoma, and that within this continuum there are no clearly recognizable dividing lines. In 40 percent of the specimens studied, multiple invasive sites were found, many in widely different parts of the breast. On the basis of these and other data we have concluded that carcinoma of the breast is a diffuse disease of mammary epithelium and that the histologic expression of the disease varies from place to place.

Reasoning further from this concept, we theorized that there exists a stage in the development of breast cancer at which invasion has not occurred or is so slight in extent that the probability of metastasis is nonexistent. An analogous lesion is carcinoma *in situ* or microinvasive carcinoma of the uterine cervix. Such a lesion should have a high rate of curability by local measures alone. The terms "early" breast cancer and "occult" breast cancer are inadequate to express this concept. "Early" breast cancer has, in common medical parlance, come to mean simply a mass lesion in the breast without palpable lymph node metastasis. Sizeable masses, however, may be present without palpable lymph nodes, and the probability of systemic dissemination increases with the size of the invasive mass. Furthermore, the word "early" implies a knowledge of time-growth relationship which does not exist. "Occult" breast cancer is usually understood to mean a carcinoma which is demonstrable mammographically but is not palpable. Masses of considerable dimension can be undetectable by palpation in large breasts. Even in breasts of average size a malignant mass can be obscured by the presence of cysts or other thickenings. Thus, while noninvasive and microinvasive carcinomas are occult, fully invasive lesions may be occult also.

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To avoid these difficulties, we introduced in 1971 the designation "minimal" breast cancer.[4–6] This term was defined as including *in situ* lobular carcinoma, noninvasive intraductal carcinoma, and invasive carcinoma forming a mass no greater than 0.5 cm in diameter. This upper limit of size was established by extrapolation from a study relating volume of invasive masses to the probability of axillary lymph node or other metastasis. An invasive mass of this volume, it was calculated, should have at most a ten percent probability of having produced dissemination. It was felt proper to include intraductal, intralobular, and microinvasive carcinoma in one category since it has been well established both by our own work and that of Ozzello[7,8] that histologic criteria for the evaluation of invasion in mammary carcinoma are less than precise.

It was predicted that lesions falling into the minimal breast carcinoma category would have a curability rate in excess of 90 percent. A recent report by Wanebo *et al.*[9] indicates that this prediction was, if anything, pessimistic. In a series of patients with minimal breast carcinoma treated by modified radical mastectomy, the five year survival rate was 97 percent and the ten year survival rate 95 percent. More recently, Westbrook and Gallager[10] have reported a retrospective study of patients with intraductal carcinoma only. Among the 64 patients in the series there were no deaths due to breast cancer in five to 15 years. Only one patient had a local recurrence and only one had positive axillary lymph nodes. The patients in this group were treated by a variety of methods.

The last year has seen the establishment of 29 geographically distributed breast cancer screening centers, sponsored jointly by the American Cancer Society and the National Cancer Institute. Not only are these centers discovering breast cancer at a rate higher than that which was anticipated, but an unexpectedly high percentage of the lesions being found are in the minimal breast carcinoma category. There is, therefore, current need for better understanding of the optimal treatment of minimal breast cancer. The optimal treatment would be that which would achieve the highest survival rate and at the same time produce the best cosmetic result possible. It is clear from the work cited above that modified radical mastectomy is adequate in the first respect. It seems probable that extended simple mastectomy with low axillary dissection would also be satisfactory. One suspects, however, that more conservative methods might be equally effective in this localized stage of disease.

There is ample justification for suggesting clinical trials of radiation therapy in the treatment of minimal breast cancer. It has long been known that irradiation is capable of sterilizing lesions considerably greater in extent. Among a group of breast carcinoma

TABLE I*

HISTOLOGIC FINDINGS

Status of Tumor after Radiation Therapy	No.	Percent
No morphologic change	6	12
Cytoplasmic changes only	14	27
Nuclear and cytoplasmic changes	24	46
No residual neoplasm	8	15

* Histologic findings in 52 primary breast carcinomas treated by preoperative irradiation. Preirradiation diagnoses were established by needle biopsy only. In each case the tumor was greater than 5 cm in diameter or was associated with other grave signs.

Table II*

Status of Axilla before Radiation Therapy	No. of Cases	No. Expected to Be Positive	No. Observed to Be Positive	Ratio O/E
Single enlarged lymph node less than 2.5 cm	100	67	30	0.45
2 or more enlarged lymph nodes, smaller than 2.5 cm	118	79	46	0.58
1 or more enlarged lymph nodes larger than 2.5 cm	27	24	17	0.71

* Effect of volume of metastatic disease on response to radiation therapy in 245 breast cancer patients with clinically positive axillary lymph nodes.

patients treated by preoperative irradiation, we have studied a subgroup known to have had invasive masses present at the time irradiation was begun (Table I). All of these had had their diagnoses established by needle biopsy only. In 15 percent of the patients in this group, histologic examination of the postirradiated mastectomy specimens revealed no recognizable residual carcinoma, in spite of the fact that many of these patients had originally had masses greater than 5 cm in diameter. In an additional 46 percent of specimens, the neoplastic cells showed nuclear fragmentation or pyknosis, indicating that the cells probably were not viable. Thus the sterilization rate produced in these relatively large lesions was on the order of 60 percent.

The biologic characteristics of minimal breast cancer are such as to make radiation therapy a logical candidate for a primary treatment modality. Irradiation is most effective when the tumor burden is small. Confirmation of this has been obtained from another study of preoperatively irradiated breast carcinomas. In this group, the incidence of positive axillary lymph nodes after irradiation was lower than anticipated when only one or two small clinically positive lymph nodes had been present prior to treatment. When multiple lymph nodes were involved, or when the lymph nodes were large, the number of histologically demonstrated metastases much more closely approached the expected number (Table II). Since in minimal breast cancer the number of neoplastic cells present is originally small, and since it is usually still further reduced by the biopsy necessary for diagnosis, the situation offers favorable circumstances for the application of radiation therapy.

It would be naive to assume that invasive, mass-forming breast cancer will in the future disappear simply because of the availability of detection techniques and screening centers. Advanced uterine cervical cancer, after all, is still being seen 25 years and more after the work of Papanicolaou provided a means of making it an extinct disease. Studies aimed at determining the optimal treatment for invasive breast cancer are, therefore, appropriate and justifiable. It is unlikely, however, that any manipulation of therapeutic modalities will greatly alter the mortality of invasive breast cancer. The best immediate opportunity for a significant reduction in breast cancer mortality lies in further development of means for detection of minimal breast cancer and in studies designed to determine how best to treat it.

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Vol. 126, No. 1

TREATMENT, RESULTS AND PROGNOSTIC FACTORS IN STAGE I AND II SARCOMAS OF THE CORPUS UTERI*

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ABSTRACT:

One-hundred and four cases of Stage I and II uterine sarcomas treated at Roswell Park Memorial Institute over a 27 year period are reviewed. Included are 30 cases of mixed mesodermal tumor, 27 cases of carcinosarcoma, 25 cases of endometrial stromal sarcoma, and 22 cases of leiomyosarcoma. Prognostic factors were found to include histologic classification, stage, uterine size, depth of myometrial invasion, and type of treatment. Endometrial stromal sarcomas had the best over-all prognosis. Radiation therapy alone was inadequate treatment, but was of adjunctive value to surgery in terms of increasing survival and decreasing pelvic recurrences in patients with endometrial stromal sarcoma, mixed mesodermal tumor, and carcinosarcoma. Patients with leiomyosarcoma did not benefit from adjunctive radiation therapy.

WHETHER or not radiation therapy is of adjunctive value in the treatment of surgically resectable uterine sarcomas has long been the subject of debate. The number of cases treated at any one institution is small, so the controversy suffers from anecdotal reporting, series of statistically insignificant numbers, and lack of meaningful data on radiotherapeutic techniques. In addition, there has been a tendency to include the different histologic types of these lesions under the heading "uterine sarcoma" and speak of them as one when discussing therapy. There has also been a notable failure to consider other potentially prognostic factors such as stage, mitotic activity, uterine size, and depth of myometrial invasion which, in addition to therapy, may also help to determine the patient's final outcome. This paper describes our experience with 104 cases of Stage I and II uterine sarcomas in which an attempt has been made to account for these factors as much as possible and thereby to state more accurately which, if any, uterine sarcoma patients are significantly benefited by radiation therapy.

MATERIAL AND METHOD

During the years 1945 through 1972, 115 cases of Stage I and II uterine sarcomas were treated at Roswell Park Memorial Institute. Eleven of these cases were excluded from this study either because of inadequate follow-up or, on review of the histologic material, the tumors were reclassified as poorly differentiated adenocarcinoma or did not contain sufficient mitotic activity to permit classifying them as sarcomas. Of the 104 remaining cases, 87 were Stage I and 17 were Stage II. There were 30 cases of mixed mesodermal tumor (containing heterologous elements), 27 cases of carcinosarcoma (homologous elements only), 25 cases of endometrial stromal sarcoma, and 22 cases of leiomyosarcoma (Table I).

The data collected from clinical records

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TABLE I

HISTOLOGY ACCORDING TO STAGE

	Stage I	Stage II	Total
Mixed mesodermal sarcoma	22	8	30
Carcinosarcoma	22	5	27
Leiomyosarcoma	19	3	22
Endometrial stromal sarcoma	24	1	25
Total	87	17	104

were analyzed on a Univac Spectra 70/3 Electronic Digital Computer. The Life Table Method was used to study survival, and all figures were submitted to the Breslow, chi-square test for statistical significance. A significance level of five percent was used as the maximum.

CLINICAL FINDINGS

Ages of the patients ranged from 21 to 95 years with a mean age of 58. None of the subgroups differed significantly from this mean age.

The vast majority of patients presented with abnormal vaginal bleeding. Vaginal discharge was another common complaint, but pelvic pain and bladder and bowel problems were infrequent in these early-stage sarcomas.

Because this paper concerns itself only with Stage I and Stage II disease, no patients had evidence of tumor spread outside the uterus on physical examination. Twenty-eight patients (27 percent) had uteri considered to be normal-sized and 76 patients (73 percent) had enlarged uteri, 19 (18 percent) of which were markedly enlarged (greater than eight week pregnancy size).

Eleven of the 17 patients with Stage II disease had grossly visible cervical tumors. In the remaining six cases, the diagnosis of cervical involvement was made by punch or cone biopsy or endocervical curettage.

PATHOLOGIC FINDINGS

The types of uterine sarcomas encountered and their numbers are noted in Table I. All cases of endolymphatic stromal myosis and cellular myomas were eliminated from this study. These lesions, according to Norris and Taylor[7,11] are differentiated from endometrial stromal tumors and leiomyosarcomas respectively by virtue of containing less than ten mitoses per ten high-power microscopic fields. They behave in a fashion much less aggressive than their more malignant counterparts.

There was no discrepancy between those tumors diagnosed clinically as Stage II lesions (cervix involvement) and the findings on pathologic examination where hysterectomy specimens were available. Sixteen percent of the entire group (17/104) were verified as being Stage II (Table I). Twenty-seven percent of mixed mesodermal tumors (8/30), 19 percent of carcinosarcomas (5/27), 14 percent of leiomyosarcomas (3/22), and four percent of endometrial

TABLE II

HISTOLOGY ACCORDING TO MYOMETRIAL INVASION*

		Myometrial Invasion		
		$<\frac{1}{2}$	$>\frac{1}{2}$	Serosa
Mixed mesodermal sarcoma	30	5	12	0
Carcinosarcoma	27	10	4	3
Leiomyosarcoma	22	0	18	3
Endometrial stromal sarcoma	25	4	8	3
Total	104	19 (27 percent)	42 (60 percent)	9 (13 percent)

* A very highly significant relationship was found between sarcoma and myometrial invasion, $P < 0.002$.

stromal sarcomas (1/25) had spread to involve the cervix.

Depth of myometrial involvement was studied in 70 cases. In twelve patients receiving radiation therapy alone, no pathologic specimens were available, and in seven cases the histologic material was not sufficient to judge the depth of myometrial invasion. In 15 patients preoperative irradiation was delivered, and since this may have altered the amount of uterine wall involvement, these cases were excluded in order to make an accurate prediction of prognosis on this basis. It can be seen from Table II that deep myometrial invasion was the rule for these highly malignant lesions. Seventy-three percent (51/70) invaded to a depth greater than half the thickness of the uterine wall. Leiomyosarcoma, expectedly, was the worst offender since this lesion tends to arise within the myometrium itself.

In seven of the 104 cases (seven percent), tumor was found outside the uterus at the time of laparotomy or during examination of the pathologic specimen. The three extrauterine structures involved were ovary, pelvic lymph nodes, and pelvic peritoneum. Three of these cases were carcinosarcomas, two mixed mesodermal sarcomas, and one each endometrial stromal sarcoma and leiomyosarcoma.

TREATMENT

Sixty-one patients had surgery alone for the treatment of their sarcomas, 31 patients had either pre- or postoperative irradiation, and twelve patients had radiation therapy alone (Table III). Almost all patients undergoing surgery had total abdominal hysterectomy and bilateral salpingo-oophorectomy. A few patients had an incomplete procedure in the form of subtotal hysterectomy or failure to remove one or both ovaries.

Of the 15 patients receiving preoperative radiation therapy, 14 had radium alone. Five to six thousand mg-hrs were given in all cases either in the form of multiple intrauterine tubes and vaginal cylinder or by tandem and ovoids. One patient received 3,000 rads in three weeks of whole-pelvis radiation and 4,000 mg-hrs by intracavitary radium.

Table III

TREATMENT ACCORDING TO STAGE

	Stage		Total
	I	II	
Surgery alone	54	7	61
Preoperative irradiation	14	1	15
Postoperative irradiation	14	2	16
Radiation therapy alone	5	7	12
Total	87	17	104

Sixteen patients received postoperative irradiation. In eight cases this was external alone consisting of approximately 4,000 rads in four weeks to the whole pelvis. In three cases only intravaginal ovoids were used delivering 3,000 rads to the 0.5 cm depth. Five patients received both external irradiation (3,000 rads) and intravaginal radium (3,000 rads at 0.5 cm depth).

Of the twelve patients receiving only radiation therapy for their disease, four had radium alone with a total dosage of between 6,000–7,000 mg-hrs, four other patients received only external irradiation (4,000–5,000 rads), and four patients had external and intracavitary therapy consisting of 4,000 rads to the whole pelvis and 4,000 mg-hrs *via* radium.

RESULTS

Survival versus histology. The two and five year survival rates for the four different types of uterine sarcomas are listed in Table IV (Fig. 1). The five year survival for endometrial stromal sarcoma was 62 percent, carcinosarcoma 41 percent, leiomyosarcoma 39 percent, and mixed mesodermal sarcoma 31 percent. Although these figures did not withstand the Breslow test of statistical significance, there is a strong suggestion that the prognosis for endometrial stromal sarcoma was better than for the other three histologic types. The respective

Table IV

SURVIVAL *versus* TYPE OF SARCOMA

Histology	Percent Survival	
	2 year	5 year
Mixed mesodermal sarcoma (30)	55	31
Carcinosarcoma (27)	69	41
Endometrial stromal sarcoma (25)	67	62
Leiomyosarcoma (22)	57	39
Over-all (104 patients)	62	42

two and five year over-all survivals of 62 percent and 42 percent belie the oft-expressed opinion that two year survival in uterine sarcomas portends a good prognosis.

Survival versus stage, uterine size, myometrial invasion, and spread to extrauterine structures. Five year cumulative survival among the 87 Stage I patients was 45 percent compared to 30 percent for the 17 patients with Stage II (Fig. 2). These figures help to confirm the validity of the FIGO (International Federation of Gynecology and Obstetrics) classification for uterine sarcomas, a staging system initially devised for use in adenocarcinoma of the endometrium.

Survival was inversely proportional to uterine size (Fig. 3). Fifty-three percent of the 28 patients with normal-sized uteri survived five years. Of the 57 patients with moderately enlarged uteri, 43 percent survived, and only 21 percent of 19 patients with markedly enlarged uteri survived.

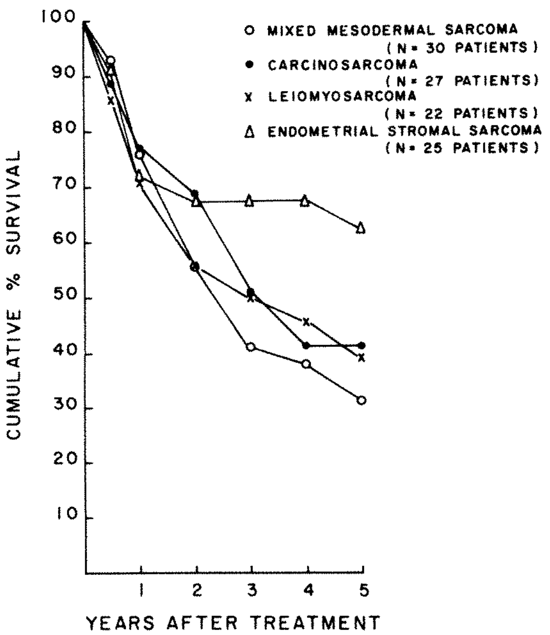

Fig. 1. Uterine sarcoma: survival *versus* histology. Comparison of survival according to histology. The five year survival for endometrial stromal sarcoma was better than the other three histologic types.

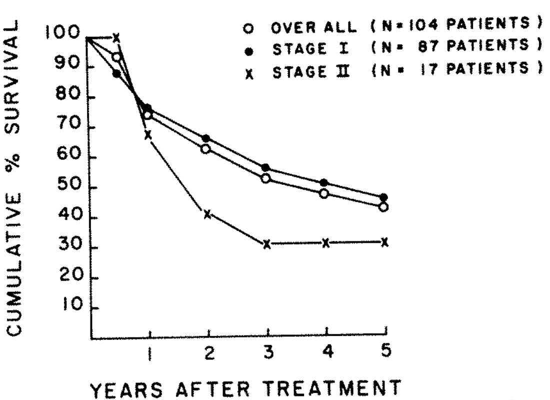

Fig. 2. Survival *versus* stage: uterine sarcoma, Stage I and II. Confirm the validity of the FIGO classification for uterine sarcomas, a staging system initially devised for use in adenocarcinoma of the endometrium.

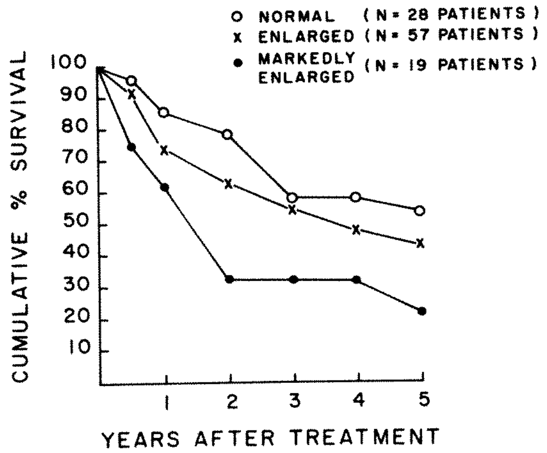

Fig. 3. Uterine sarcoma: survival *versus* uterine size. Normal-sized uteri have a better survival than enlarged uteri.

Depth of myometrial invasion also appeared to be prognostically important (Fig. 4). Of 19 patients with less than one-half of the uterine wall involved, 58 percent survived five years. However, of the 51 patients with deeper invasion, only 29 percent survived.

Interestingly, three of the seven patients (43 percent) with preoperatively unsuspected involvement outside the uterus survived five years, the same as for the entire group.

Survival versus treatment. The cumulative five year survival rates for Stage I patients, Stage II patients, and the combined group are recorded in Table V as a function of treatment. It appears that the five year over-all survival for surgery plus radiation therapy (53 percent) was better than that for surgery alone (40 percent), which in turn was superior to radiation alone (29 percent); (these figures fall short of statistical significance). If one looks at Stage I disease only, there was only a small difference between surgery and surgery plus irradiation. No difference was noted between patients receiving preoperative irradiation and those receiving postoperative irradiation. Another observation is that surgery without supplemental irradiation was completely ineffective in the treatment of Stage II sarcoma.

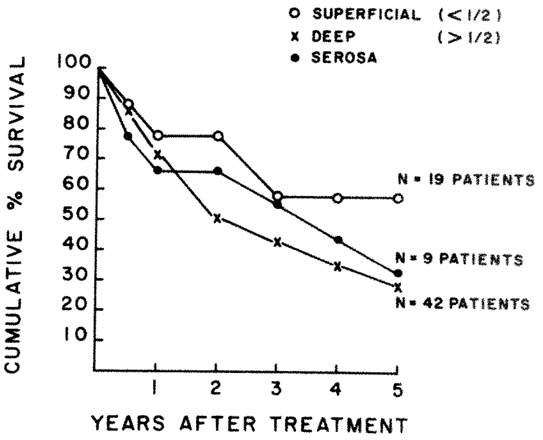

Fig. 4. Uterine sarcoma: survival *versus* depth of myometrial invasion. Deep myometrial invasion has a lower survival than superficial invasion.

In Table VI, survival for each histologic type is matched against treatment. Although again the numbers do not reach statistical significance, some inferences can be made. Patients with endometrial stromal sarcoma did better than the other histologic groups regardless of therapy and the 78 percent survival among endometrial stromal sarcoma patients receiving surgery plus irradiation was better than the 60 percent for those patients having surgery alone. Surgery plus irradiation also appeared to improve survival in mixed mesodermal and carcinosarcoma patients. None of three leiomyosarcoma patients having surgery plus irradiation survived, but 46 percent of 18 patients having surgery alone did, ($p<0.05$). The figures suggest that adjunctive radiation therapy is of value in all but the leiomyosarcoma patients.

Recurrences. Also important in determining the best mode of therapy in this disease

Table V

SURVIVAL *versus* TREATMENT, ALL SARCOMAS

Treatment	Percent 5 Year Survival		
	Stage I	Stage II	Over-all
Surgery alone (61)	45 (54)	0 (7)	40
Preoperative irradiation (15)	51 (14)	NED at 2 yr. (1)	54
Postoperative irradiation (16)	54 (14)	100 (2)	53
Irradiation alone (12)	20 (5)	38 (7)	29

( ) = Number of patients.
NED = No evidence of disease.

TABLE VI

5 YEAR SURVIVAL *versus* HISTOLOGY ACCORDING TO TREATMENT

Histology	Percent 5 Year Survival		
	Surgery Alone	Surgery and Irradiation	Irradiation Alone
Mixed mesodermal sarcoma	26 (19)	40 (5)	33 (6)
Carcinosarcoma	36 (10)	57 (14)	0 (3)
Endometrial stromal sarcoma	60 (14)	78 (9)	50 (2)
Leiomyosarcoma	46 (18)	0 (3)	0 (1)

(   ) = Number of patients.

are the incidence and pattern of tumor recurrences. Of the total of 104 cases, 68 (65 percent) recurred, 62 percent of the Stage I lesions and 82 percent of Stage II. Of these 68 patients, 51 percent had their initial recurrence in the pelvis and 21 percent had recurrences in the pelvis plus some distant site. The remaining 28 percent recurred at distant sites only, most commonly the lungs and abdomen. There were no significant differences in the recurrence patterns among the different histologic types, even leiomyosarcoma. Seventy-two percent of recurrence occurred within two years (Fig. 5).

If one considers all cases which recurred in the pelvis as local treatment failures, it can be seen from Table VII that the 26 percent failure rate for surgery plus pre- or postoperative irradiation was far better than for surgery or radiation therapy alone (57 percent and 50 percent, respectively), $p < 0.005$. This would seem to indicate that surgery plus irradiation provides better local control in the treatment of uterine sarcoma than either modality alone (Fig. 6).

Fourteen of the 43 patients receiving some form of radiation therapy (either alone or in conjunction with surgery) recurred in the pelvis. Five of these cases were among those patients receiving external irradiation alone, five were derived from patients having brachytherapy alone, and four were among those having both external and internal treatment. In other words, no specific form of radiation therapy appeared to offer superior results in reducing pelvic recurrences.

DISCUSSION

Only 104 verified cases of Stage I and II uterine sarcomas were seen over a 27 year period at Roswell Park Memorial Institute, a major cancer treatment center. This illustrates the difficulty in assembling a sufficient number of these cases on which to base valid conclusions. Even though several of our results are highly suggestive, many of them fall short of statistical significance, even though this is one of the largest reported series of early-stage uterine sarcomas accumulated at one institution.

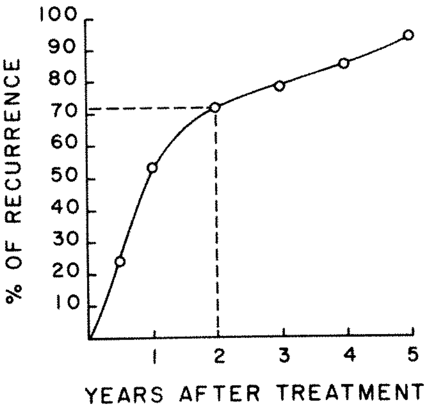

FIG. 5. Uterine sarcoma: recurrence and time of detection. Seventy-two percent recurred within two years.

Table VII

SITE OF RECURRENCE *versus* TREATMENT

Treatment	Site of Recurrence		
	Pelvis (Percent)	Distant Only (Percent)	Total (Percent)
Surgery alone (61)	57	15	72
Surgery plus irradiation (31)	26	29	55
Irradiation alone (12)	50	8	58

That uterine sarcomas behave in a more malignant fashion than endometrial adenocarcinoma is suggested by the fact that even in these early-stage lesions, 73 percent of the uteri were enlarged and 73 percent of the tumors had invaded to a depth greater than one-half the myometrial thickness. In a typical, large series of patients with adenocarcinoma of the endometrium,[10] 31 percent had uterine enlargement and only 18 percent had deep myometrial involvement.

Histology influences survival in patients with uterine sarcoma. Endometrial stromal sarcoma had a better prognosis in our series, 62 percent of these patients surviving five years as opposed to 41 percent or less for the remaining histologic types. Other authors have also noted this improved survival for endometrial stromal sarcoma patients.[2,5,7] It has been suggested previously that mixed Müllerian tumors containing homologous elements only (carcinosarcoma) have a better prognosis than those containing heterologous elements (mixed mesodermal tumor).[2,6,8] Forty-one percent of our carcinosarcoma patients survived five years as opposed to 31 percent for mixed mesodermal sarcoma. Survival figures for leiomyosarcoma have ranged from 0 to 59 percent and this disparity probably stems from failure to exclude cellular leiomyomas from some series.[1] Our five year survival was 39 percent in Stage I and II leiomyosarcoma patients to which strict histologic criteria were applied.

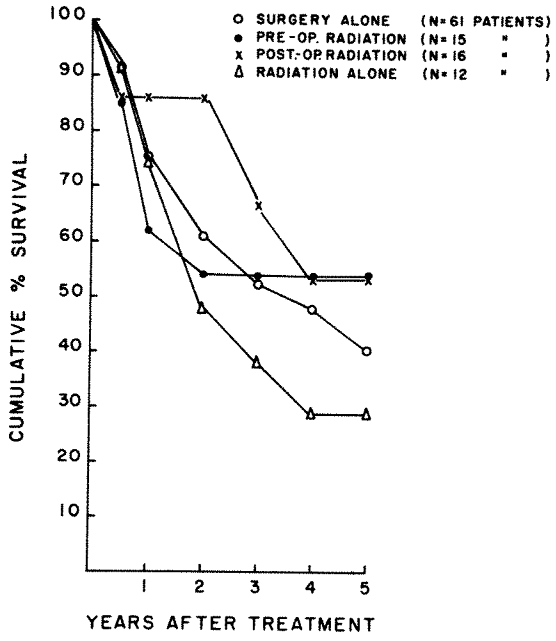

Fig. 6. Uterine sarcoma, Stage I and II; survival *versus* type of treatment. Surgery plus irradiation provides better control than either alone.

Cervix involvement, uterine size, and depth of myometrial invasion are known to influence prognosis in patients with adenocarcinoma of the endometrium. These factors have largely been ignored, however, in previous papers dealing with uterine sarcomas. Among our patients with Stage I disease, survival was 45 percent compared to 30 percent for patients whose tumors involved the cervix (Stage II). Fifty-three percent of patients with normal-sized uteri survived five years, but only 43 percent of those with moderately enlarged uteri and 21 percent of those with marked uterine enlargement did as well. Depth of mymetrial invasion was also significant in that 58 percent of patients with less than one-half of the uterine wall involved survived as opposed to only 29 percent with deeper invasion. These factors therefore appear to be important determinants in the prognostic consideration of nonmetastatic uterine sarcoma.

Seven of 104 sarcoma patients (seven percent) had extrauterine tumor involvement at the time of laparotomy. Of the three five year survivors in this group, one patient had an ovarian metastasis and received surgery plus preoperative irradiation, another had gross involvement of the left obturator lymph nodes which were excised and supplemental, postoperative pelvic irradiation given, and the third patient, who had an implant on the right broad ligament, had surgical excision of this but no form of irradiation. No conclusions can be drawn from this small number of patients, but it would seem that those patients having pelvic tumor outside the uterus at the time of laparotomy should probably receive pelvic irradiation to tolerance postoperatively if they have not already.

That irradiation alone is not adequate primary therapy for sarcoma of the uterus is now well-recognized.[2] Twelve patients in our series who received only irradiation for their disease had far inferior results compared to those patients who received hysterectomy. The question, then, is whether radiation therapy is of *adjunctive* value in the treatment of uterine sarcomas. Edwards, in 1969,[4] reported the experience at the M. D. Anderson Hospital over 21 years. Fifty-two percent of 29 patients with localized disease treated with preoperative irradiation survived as compared to 30 percent of 21 patients treated by surgery alone. This improved survival with irradiation was true for all the histologic subgroups except leiomyosarcoma. The amount of tumor remaining in the excised uterus was less in the group receiving preoperative irradiation and in ten of these cases no residual tumor at all was present, demonstrating the ability of irradiation to destroy sarcomatous tissue.

Belgrad *et al.*,[2] combining their experience with that of three other major institutions, found that two year survival was improved by pre- or postoperative irradiation in mixed Müllerian tumors (35 percent for surgery plus irradiation *versus* 20 percent for surgery alone) and especially in endometrial stromal sarcoma (57 percent *versus* 37 percent), but not in patients with leiomyosarcoma.

Our results are entirely supportive of the conclusions reached in these two papers. Over-all five-year survival in 31 patients receiving either preoperative or postoperative irradiation was 53 percent compared with 40 percent for patients having surgery alone. Leiomyosarcoma patients responded better to surgery alone, but endometrial stromal sarcomas, carcinosarcomas, and mixed mesodermal sarcomas all demonstrated improved survival with the combined therapy (Table VI). Of possibly equal significance is the fact that local treatment failures (*i.e.*, pelvic recurrences) were less than half for the irradiated group than for those having surgery alone (26 percent *versus* 57 percent).

In view of these statistics, our present treatment regimen for patients with Stage I and II uterine sarcomas other than leiomyosarcomas consists of preoperative irradiation followed by total abdominal hysterectomy and bilateral salpingo-oophorectomy. In Stage I disease this consists of intracavitary radium only, but in Stage II lesions, where the chance for lymphatic spread is greater, external pelvic irradiation is added. If, after surgery, deep myometrial invasion or extrauterine pelvic involvement is noted, supplemental irradiation can be given. In general, for leiomyosarcoma patients, therapy consists of surgery without adjunctive radiation therapy.

Recently, in a further attempt to increase survival and decrease distant, as well as local, recurrences in patients with early-stage uterine sarcomas, we have initiated a treatment protocol incorporating adriamycin• chemotherapy as a third modality of treatment in conjunction with surgery and irradiation. Adriamycin is given concurrently with initial radiation therapy and continued in monthly courses for six months. It has been demonstrated that adriamycin is active against sarcomas[3,9] and there has been work to indicate that it sensitizes cancerous tissue to the destructive effects of irradiation by preventing repair of broken nucleic acid helices.[12]

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IRRADIATION OF ENDOMETRIAL CANCER IN PATIENTS WITH MEDICAL CONTRAINDICATION TO SURGERY OR WITH UNRESECTABLE LESIONS[*]

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ABSTRACT:

In 124 medically inoperable patients with endometrial cancer, the five and ten year actuarial survival rates were 68 percent and 57 percent. In 26 patients with technically unresectable endometrial cancer, 26 percent actuarial survival rates at both five and ten years were seen. Pelvic control at death was 89 percent in Stage Ia, 78 percent in Stage Ib, 82 percent in Stage II, and 62 percent in Stage III. Sophisticated intracavitary therapy alone or in conjunction with external irradiation appears to give better uterine control rates than does external irradiation alone.

IN spite of the fact that Heyman[3] and later Kottmeier[4] have noted that there is a sizable group of patients with endometrial cancer who are not suitable for surgical procedures, the recent literature contains little specific information on the proper therapy for such patients. This paper reviews a series of these patients who were treated by irradiation alone because of various medical contraindications to surgical procedures or because the disease was too extensive for surgical resection.

PATIENT POPULATION

From 1948 through December, 1969, definitive treatment by irradiation alone was completed at M. D. Anderson Hospital on 150 patients with endometrial cancer who were not suitable for surgical procedures. One hundred and twenty-four were inoperable for various medical reasons (Table I), and 26 were not suitable for surgical procedures because disease extended beyond the uterine corpus and cervix. Some patients listed as having technically unresectable lesions were in fact also medically inoperable. These 150 constitute about 20 percent of the patients with endometrial cancer treated with curative intent during this time period at the institution. The average patient age was 66.5 years (range, 30 to 89 years); 104 were white, 40 Black, and six other races. All patients had biopsy-proved adenocarcinoma before treatment, and all patients have been followed for a minimum of five years. The cases have been staged retrospectively according to a modification of the current FIGO (International Federation of Gynecology and Obstetrics) classification (Table II).[1]

MEDICALLY INOPERABLE PATIENTS

TREATMENT

Stage I. The treatment techniques have undergone a gradual evolution and have been published.[2] Intracavitary radium applications were used alone in 76 patients and were used in conjunction with external

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irradiation in nine patients. One patient was treated with only external irradiation (Table III).

The intrauterine irradiation has been done by means of Heyman packing, except in small uterine cavities which admitted only sources in tandem. Originally, the treatment times were based on Heyman's timetable or a maximum of 2,000 milligram hours (mghrs) for each of two applications separated by three weeks. In 1958, each packing was increased to 2,500 mghrs because of good tolerance. Subsequently, 3,000 mghrs have been used for each insertion. In very large cavities, three individual packings separated by two weeks each have been utilized to deliver 6,000–8,000 mghrs. A tandem alone has been used when the uterine cavity was narrow and would only accept sources in tandem. At first, two 48 hour applications were done three weeks apart, using tandems loaded, for example, 20–15–10 mg or 20–15 mg. Subsequently, this has been increased to two 72 hour tandems, or a maximum of 6,000 mghrs. In this series, an average uterine dose of approximately 6,000 mghrs was given to all Stage I cases treated by radium only.

Until 1952, vaginal irradiation was done by means of plastic ovoids concomitant with the first Heyman packing and a vaginal cylinder with the second Heyman packing, delivering a total of about 6,500 rads vault surface dose. Then, until 1957, a single-piece applicator consisting of ovoids and cylinder was used in a separate insertion to deliver 5,500–7,200 rads surface dose. This technique was abandoned because of complications and because it became apparent that the lower portion of the vagina did not require treatment. Thereafter, ovoids with rigid handles or protruding tandem sources have been utilized with each intrauterine application. In this study, vaginal vault surface doses averaged approximately 7,500 rads in those Stage I cases treated by radium only.

Stage II. Patients with Stage II disease (*corpus et collum*) were treated mainly by radium only in the early years of the series, although an occasional patient with a large cervical disease component also received external irradiation. Beginning in 1964, each patient with a Stage II lesion sys-

TABLE I

CRITERIA FOR MEDICAL INOPERABILITY*

	No. of Cases
Significant obesity (usually >200 lb.)	72
Hypertension	56
Heart disease	34
Old age (>75 years)	32
Diabetes mellitus	29
Refused or did not return for planned surgery	4
Other medical contraindications	21

* Many patients had more than one criterion.

TABLE II

ENDOMETRIAL CANCER STAGING CLASSIFICATION*

Stage I:	Carcinoma confined to the corpus
Ia:	The length of the uterine cavity is 8 cm or less
Ib:	The length of the uterine cavity is more than 8 cm
Stage II:	Carcinoma has involved the corpus and cervix
Stage III:	Carcinoma has extended outside the corpus and cervix, but not outside the true pelvis
Stage IV:	Carcinoma has extended outside the true pelvis or has obviously involved the mucosa of the bladder or rectum

* Modified from the FIGO Classification.[1]

TABLE III

METHODS OF IRRADIATION

Stage	Radium Only	External Irradiation + Radium	External Irradiation Only
Medically Inoperable Patients			
Ia	40	5	—
Ib	36	4	1
II	19	18	1
Patients with Technically Unresectable Lesions			
III	6	12	6
IV	—	1	1

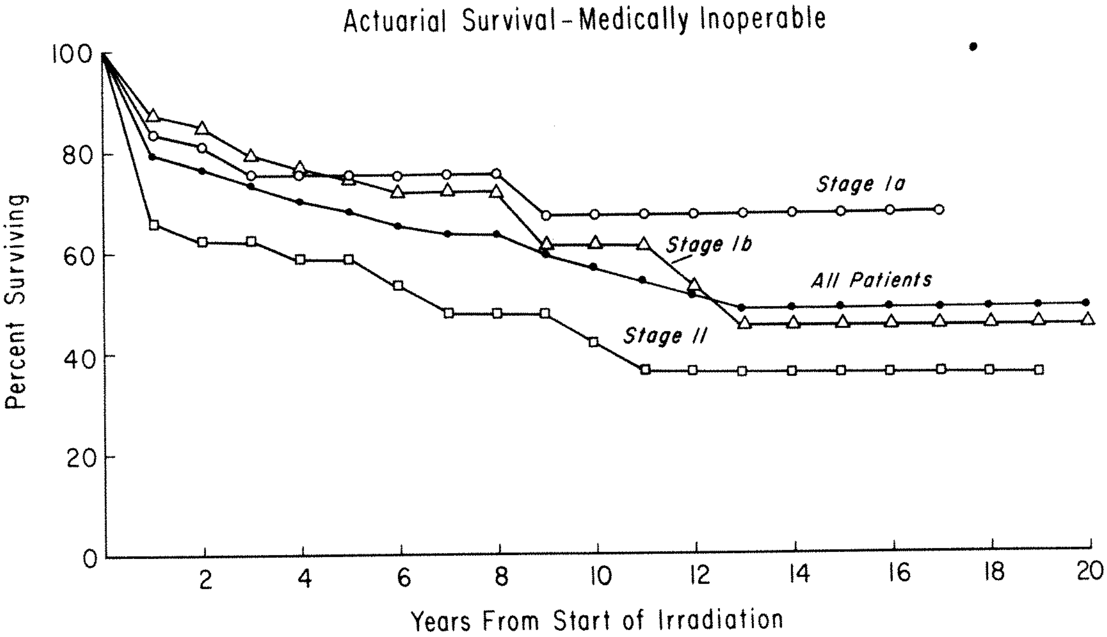

FIG. 1. Actuarial survival rate curves for medically inoperable patients, as calculated by the Bergson-Gage Life Table method. (Patients dead of intercurrent disease and those lost to follow-up are counted as having a one-half chance of cancer death. Those dead of unknown cause are counted as dead of cancer.)

tematically received external irradiation, usually 4,000 rads delivered prior to radium through parallel opposed anterior and posterior 15×15 cm 22 MeV roentgen ray whole pelvis portals. This treatment is similar to that for primary cervical cancer. The external irradiation was utilized to treat the pelvic lymphatics, which are more likely to contain metastatic tumor when the cervix is involved by endometrial cancer.

In the 19 patients treated by radium only, an average of 5,600 mghrs were delivered to the uterus and an 8,700 rad surface dose to the vagina. In the 18 patients treated by 4,000 rads with external irradiation, the subsequent radium applications delivered about 3,500 mghrs to the uterus and a 5,500–6,000 rad surface dose to the vagina.

RESULTS

Five and ten year actuarial survival rates of 68 percent and 57 percent were found in the medically inoperable group. As expected, Stage Ia patients had the best and Stage II patients the poorest survival (Fig. 1).

Failure to control disease in the pelvis was seen at death in 11 percent of Stage Ia cases, 22 percent of Stage Ib, and 18 percent of Stage II. Only twelve patients (ten percent) had treatment failures in the uterus alone (Table IV). Six of these patients were successfully retreated, four by intracavitary radium, one by hysterectomy and one by radium and hysterectomy (Table V). Pelvic failures other than in the uterus were rare.

Fifty-six patients died of intercurrent disease. In the 38 patients dying because of tumor, 27 had distant metastases alone or associated with pelvic disease.

PATIENTS WITH TECHNICALLY UNRESECTABLE LESIONS

TREATMENT

The majority of these patients was treated at least in part by external irradiation (Table III). Seven patients received external irradiation as their only therapy with an average dose of 6,000 rads in six weeks.

Table IV

FAILURE SITES IN INOPERABLE ENDOMETRIAL CANCER
1948 through 1969
(Analysis January 1975)

Stage	No. of Patients	Pelvic Disease Only			Pelvis +DM	DM Only	Dead Unknown Cause/LTF
		Uterus Only	Vagina Only	Pelvis† Only			
		Medically Inoperable Patients					
Ia	45	4*	0	0	3	5	1
Ib	41	7*	0	3	3	3	3
II	38	1	0	2	4	9	2
	124	12	0	5	10	17	6
		Patients with Unresectable Lesions					
III	24	1	4	1	3	9	0
IV	2	1	0	1	0	0	0
	26	2	4	2	3	9	0

* 2 uterine recurrences in Stage I_a and 4 in Stage I_b were successfully retreated.
† The uterus, vagina, or both, can be the site of a recurrence in addition to other pelvic structures.
DM= Distant Metastases; LTF= Lost to Follow-up.

Reduction in field size from 15×15 cm to 12×12 and 10×10 cm was made at 5,000 and 6,000 rads, respectively, in those patients receiving these high doses. In some cases, only the involved parametrial area received a booster dose after a basic 4,000 or 5,000 rads were delivered to the whole pelvis. Eleven patients received approximately 4,000 rads to whole pelvis fields before radium. The subsequent radium applications delivered about 4,000 mghrs to the uterus and an average of 6,000 rads surface dose to the vagina. Two patients received parametrial field treatment before radium. Treatment by radium only was performed in six cases, delivering an average of 5,000 mghrs to the uterus and a 11,000 rad surface dose to the vagina.

In four cases with initial vaginal involvement by tumor (one upper third and three lower third), an interstitial radium implant was used concomitantly with or sequen-

Table V

TREATMENT AND RESULTS OF RETREATED UTERINE FAILURES IN STAGE I PATIENTS

Stage	Original Uterine Treatment	Retreatment	Outcome
I_a	8,200 mghrs	2,000 mghrs	Success
I_a	5,800 mghrs	2,500 mghrs	Success
I_a	4,500 mghrs	4,800 mghrs	Failure
I_b	3,000 rads WP*+2,500 mghrs	4,600 mghrs	Success
I_b	2,700 rads WP*+2,500 mghrs	5,000 mghrs	Success
I_b	7,100 mghrs	2,100 mghrs+TAH,† BSO‡	Success
I_b	5,000 mghrs	Vaginal hysterectomy	Success
I_b	4,100 mghrs	4,000 mghrs	Failure

* WP= Whole Pelvis Irradiation.
† TAH= Total Abdominal Hysterectomy.
‡ BSO= Bilateral Salpingo-oophorectomy.

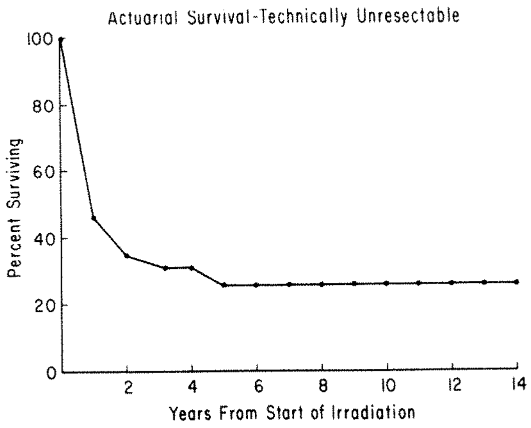

FIG. 2. Actuarial survival rate curves for patients with technically unresectable lesions, as calculated by the Bergson-Gage Life Table method.

tially to intracavitary treatment. Vaginal tumor control was successful in each case.

RESULTS

The patients with unresectable lesions had 26 percent actuarial survival rates at both five and ten years (Fig. 2).

Failure to control disease in the pelvis was seen at death in 42 percent of the total number of patients with technically unresectable lesions. Six patients had treatment failures in the uterus or vagina alone. Two uterine retreatments were attempted, but without success.

Distant metastases alone or with pelvic disease were seen in twelve of the 20 patients dying of tumor. Generalized abdominal and lung metastases were the most common.

COMPLICATIONS

The diagnosis of radiation cystitis was made in three patients one and one-half to three years after radium applications. Four necroses were seen because of high doses of radiation, one at the vaginal vault, one at the fourchette, and two in the labia. Three of these cases had been treated by an applicator encompassing the whole of the vagina and the other by a vaginal needling. All of these problems were treated conservatively.

One instance each of bowel obstruction and rectal ulceration occurred in cases receiving 7,000 rads of external irradiation as the only means of treatment.

DISCUSSION

In the entire group of patients, there were 19 (13 percent) uterine failures alone or in combination with disease elsewhere. Forty-two percent of these failures were seen by two years, 63 percent by three years, and 84 percent by five years. One patient had a uterine recurrence in the ninth year after treatment and another patient in the tenth year. All the recurrences at other pelvic sites were seen by three years.

Any clinical staging of endometrial cancer is subject to substantial inaccuracies. Thus, in attempting to draw conclusions on the efficacy of any irradiation treatment based on clinical staging alone, one must remember the inevitable inhomogeneity in the cases within any given stage and temper conclusions accordingly.

The Stage Ia cases are the most homogeneous reported in this paper, nevertheless, Figure 3 illustrates the wide range of mghr dosages used to achieve uterine control. The few uterine failures were also seen throughout a range of doses. Some of the Stage Ib lesions are large, and there are

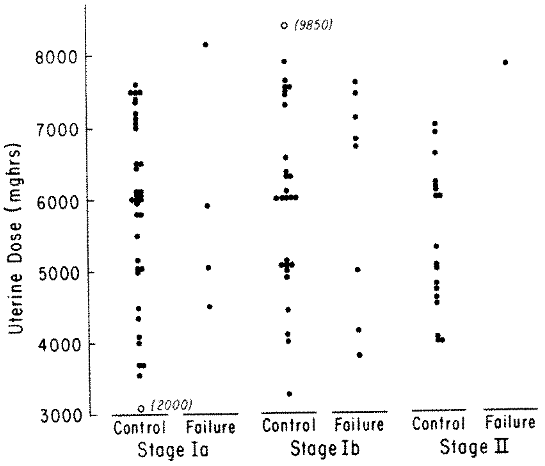

FIG. 3. Milligram-hour dose distribution by stage according to uterine control or failure in Stages I and II cases treated by radium only.

failures in the high dose range as demonstrated by the cluster of failures around 7,000 mghrs in Figure 3. Of interest is the fact that two failures receiving substantial initial treatment were, nonetheless, successfully retreated (Table v). Two of the four Stage ib and one of the five Stage ia cases treated in conjunction with external irradiation failed in the uterus. Both Stage ib cases were retrieved by further irradiation.

Only one of 19 Stage ii cases treated by radium only had treatment failure in the uterus (Fig. 3). These 19 cases received an average of 5,600 mghrs. Of 18 cases receiving 4,000 rads whole pelvis before an average of 3,500 mghrs of uterine radium, five failed in part in the uterus. These five cases did not have massive disease. It appears that when feasible, *i.e.*, when the uterine-cervical disease is not massive, sophisticated radium applications are superior to external irradiation plus diminished radium doses in definitively controlling uterine disease.

In spite of the fact that 12 of 24 of the Stage iii patients had initial involvement of the parametrium or pelvic walls, there were only two pelvic wall failures noted in these 24 (both had a frozen pelvis). Conversely, there were four failures in the uterus and five failures in the vagina in this group. Only one of these nine central failures was in the group of six patients treated by radium only. Thus, in many cases, the external irradiation seems to have been very effective in controlling parametrial or pelvic wall disease, whereas, external irradiation or external irradiation in combination with diminished doses from radium failed to control central disease in a number of patients. Although there was a tendency to use external irradiation when the disease mass was large, there is the suggestion that intracavitary radium applications are superior to high doses of external irradiation in sterilizing uterine and vaginal disease. When external irradiation is required to cover peripheral pelvic disease, it should be supplemented with one or more radium applications if feasible.

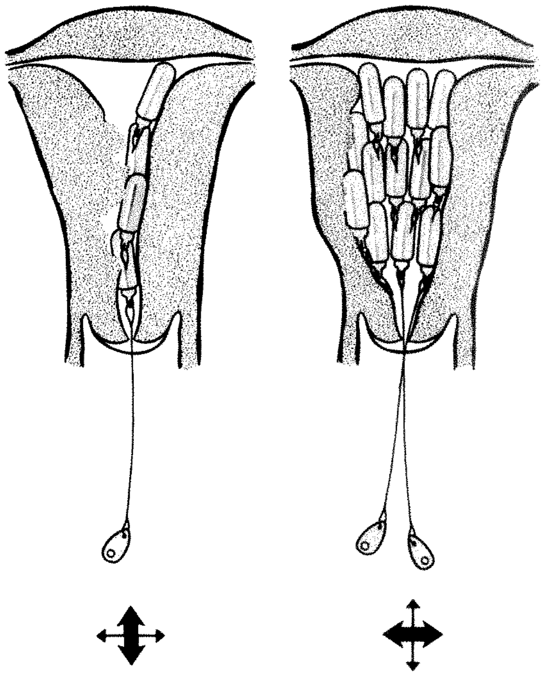

Fig. 4. Graphic illustration of the advantage of stretching the uterine cavity. (Courtesy of G. H. Fletcher, *Textbook of Radiotherapy*, Second edition, Lea & Febiger, Philadelphia, 1973, p. 676.)

Heyman[3] reported on a 1914 to 1939 series of "technically operable" although medically inoperable endometrial cancer patients treated by irradiation only. In 279 cases, a 48 percent five year absolute survival rate was obtained. In the current series of 124 medically inoperable cases, there is a 68 percent five year actuarial survival rate (Fig. 2).

The preceding data demonstrate the efficacy of irradiation used alone in inoperable cases of endometrial cancer. It is crucial in achieving high pelvic control rates in cases such as these that available techniques be adapted to the anatomic findings in each case and that definitive doses of irradiation be administered. Careful assessment of the volume of the uterine cavity is an important step in treatment planning. Evaluation of the bulk of cervix tumor and the presence or absence of vaginal or parametrial involvement, or both, are also very important in choosing the most useful treatment approach. If gentle rotation of a curved sounding probe reveals a moderate or large sized cavity, then Heyman packing is the best modality of treatment. If the cavity is large, there is an advantage to using three packings instead of two, since this permits sequential shrinkage of the tumor with more effective radium applications. Figure 4 illustrates that stretching of the uterine cavity by multiple sources thins the tumor, thereby permitting the radium to be in more effective proximity to the neoplasm. Multiple sources also permit a more uniform dose distribution. It must be stressed, however, that a good Heyman packing requires considerable care and experience. Uterine perforation with its associated problems and loss of the technique's unique advantages as mentioned above should be infrequent in the hands of an experienced operator. In the present series there were only four perforations.

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EXPERIENCE WITH TWICE-A-DAY FRACTIONATION IN CLINICAL RADIOTHERAPY*

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ABSTRACT:

Theoretical reasons have led to the treatment of 24 patients with advanced, rapidly growing squamous cell carcinomas of the head and neck, and 17 patients with inflammatory carcinoma of the breast with twice-a-day fractionation. After initial reduction in dose in both series, acute reactions and sequelae are similar to those in conventionally treated patients. The relative control rates are better than would be expected from conventional irradiation.

EVERY so often one observes continued growth of a tumor mass during a course of external irradiation. This observation is made not uncommonly in patients with squamous cell carcinomas of the upper respiratory and digestive tracts, usually growing neck lymph nodes.[5] As a rule, these patients have a short history of disease, indicating that one is dealing with a fast-growing cancer, either at the primary site or in the neck lymph nodes, or both. Initially, in some head and neck cancers, growth was arrested by adding per week two booster doses, each of 250 rads, through a small field within the treatment fields, thus giving the growing tumor mass a total weekly dose of 1,500 rads ($200\times 5+250\times 2$) for the two to four weeks. This technique can be used only if a small volume is involved, otherwise the mucosa would not tolerate continued treatment at this high weekly dose rate. Therefore, a twice-a-day hyperfractionation schedule was initiated with the purpose of increasing the irradiation effectiveness to rapidly growing tumors in the head and neck.

For patients with inflammatory carcinoma of the breast, 6,000 rads given in eight weeks followed by a booster dose (Baclesse technique) are not nearly so effective as in the noninflammatory tumors. A twice-a-day treatment scheme was designed to halve the over-all treatment time.

Although both regimens use two treatments per day, the concepts underlying the two approaches are quite different from one another.

MATERIAL AND METHOD

From April, 1972, through August, 1974, 42 patients have been treated with twice-a-day fractionation at the M. D. Anderson Hospital. The patients selected form two groups: (1) head and neck squamous cell carcinomas; and (2) inflammatory breast cancers. All treatments have been given with ^{60}Co. Portal arrangements for both head and neck and breast patients have been planned according to the techniques outlined in Fletcher's *Textbook of Radiotherapy*.[4] Almost all patients have had every field irradiated at each session.

HYPERFRACTIONATION FOR HEAD AND NECK CANCERS

The basic rationale in the treatment of

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* Presented at the Fifty-seventh Annual Meeting of the American Radium Society, Isla Verde, Puerto Rico, May 4-9, 1975.
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TABLE I

TWICE-A-DAY FRACTIONATION: SQUAMOUS CELL CARCINOMA OF THE UPPER RESPIRATORY AND DIGESTIVE TRACTS
(Analysis March, 1975)

Base of tongue	5
Nasopharynx	5
Tonsillar area	4
Pyriform sinus	2
Pharyngeal wall	2
Oral tongue	1
Floor of mouth	1
Paranasal sinuses	1
Massive postoperative recurrence	3

this group of patients was that, by doubling the number of fractions without increasing the over-all treatment time, a proportion of the rapidly dividing tumor cells surviving one dose of irradiation could redistribute themselves throughout the division cycle, moving from the resistant phases into the sensitive phases by the time of the next treatment; this is an extension of a basic concept advanced as early as 1914 by Schwarz.[8] The over-all treatment time would remain six or seven weeks and therefore there would be no increased malignant cell repopulation. Preliminary clinical experiments indicated that if, instead of one fraction of 200 rads per day, two fractions are used, about 110–120 rads per fraction will produce the same degree of reaction on the oropharyngeal mucosa. This small amount of recovery of the mucosal epithelium is in keeping with the clinical skin experiments of Dutreix *et al.*,[3] which showed that in the range of daily doses used in conventional fractionation the recovery is not so high as predicted by the theory of sublethal damage.

All but three of the 24 head and neck patients had either a T_4 primary or N_3 neck lymph nodes, or had a massive postoperative recurrence (Tables I and II). In several of the patients, the disease was so advanced that no treatment would have been attempted had it not been for the hope associated with trying a different irradiation scheme. With twice-a-day fractionation separated by eight hours (16 hours overnight), five days a week, 1,100–1,200 rads per week (110–120 rads tumor dose per fraction) were delivered. The total tumor dose, with one exception, has ranged from 6,000 to 7,500 rads in five to six and one-half weeks.

The acute mucositis across the faucial arch was plotted weekly. The mucositis grading as seen in Figure 1 very closely matched the reaction seen with 1,000 rads per week with once-a-day fractionation.[6] Three patients never developed more than a marked redness; in all others, a studded or confluent mucositis peaked in three to four weeks. Moist desquamation of the skin, usually close to the junctional area of the neck fields, occurred near the end of treatment in one-half of these patients. All reactions healed quickly after the completion of radiation therapy.

There have been three cases of late complications, one marked fibrosis, one soft tissue necrosis with bone exposure, and a fatal hemorrhage secondary to necrosis and ulceration in the site of the tumor on the pharyngeal wall. Since these complications were seen early in the study when the total dose was 7,000 to 7,500 rads (Fig. 2), the dose to subsequent patients was reduced to 6,000 to 7,000 rads. One patient who had a massive recurrence after a radical neck dissection received only 5,000 rads in 30 days because the treatment was interrupted due to carotid artery exposure.

All but four patients in the present series

TABLE II

SQUAMOUS CELL CARCINOMA OF THE UPPER RESPIRATORY AND DIGESTIVE TRACTS
(Analysis March, 1975)

	N_0	N_1	N_2	N_3
T_x	—	—	—	1
T_1	—	—	—	—
T_2	—	—	1	2
T_3	—	—	2	4
T_4	1	—	2	8

Also, massive recurrence postsurgery = 3

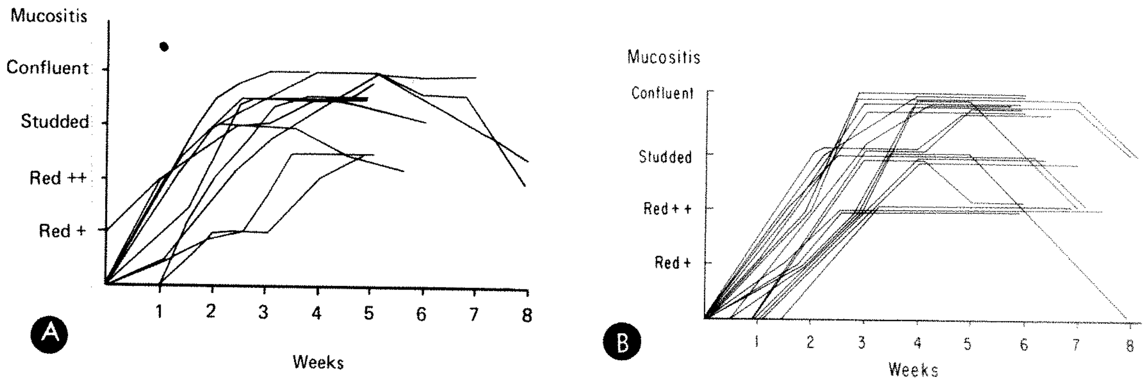

FIG. 1. (*A*) Mucositis with once-a-day fractionation at 1,000 rads/week to 5,500 rads in 5½ weeks. (*B*) Mucositis with twice-a-day fractionation, 1,100–1,200 rads/week to 6,000–7,500 rads in 5–6½ weeks. (Courtesy: Fletcher and MacComb: *Radiation Therapy in the Management of Cancer of the Oral Cavity and Oropharynx*, 1962, p. 51.)

have been followed for more than one year. The cumulative recurrence rates in patients previously treated for advanced lesions at the M. D. Anderson Hospital with either a split-course or once-a-day irradiation at 850 rads per week are compared in Table III.[5] In these advanced lesions, 94 percent (29/31) of persistence of disease or recurrence appear by one year (Table III). The cumulative recurrence rate is least with the twice-a-day scheme, despite the fact that the disease in this group of patients was, on the main, more advanced than in the other two groups (Table III).

The time-dose information has been plotted in Figure 2. Three of the five patients with recurrences have received 6,000 rads or less. A line has been hand-drawn above four of the five recurrences with the inclusion of only one controlled lesion.

Neck disease has been controlled in 18 of 24 patients. Two patients with an N_3 neck lesion had a modified neck dissection after radiation therapy. In both instances, the pathologist was unable to find evidence of any remaining malignant cells.

Despite the high control rate of local and neck disease, only six patients are currently alive without evidence of disease. Distant metastases are common in these patients with advanced cancers.

CASE I. A 53 year old white female was first seen in March, 1974, with a rapidly enlarging squamous cell carcinoma, 5 cm in diameter, of the right tonsillar area involving the base of the tongue. There were multiple bilateral neck lymph nodes, the largest measuring 6 cm, fixed in the right subdigastric area. There was also a 3 cm right parotid lymph node (Fig. 3, *A* and *B*). The staging of the lesion was T_3N_{3B}. The patient was treated with ^{60}Co twice-a-day fractionation, all fields treated at each session, 1,150 rads midline tumor dose per week, loaded 2:1 in favor of the right side. The left posterior cervical chain was treated with 7 MeV electrons to the limit of the spinal cord dose. The fields covering the primary lesion were reduced at 5,780 rads tumor dose in five weeks to 7×6 cm. The final tumor dose was 7,000 rads in 43 days.

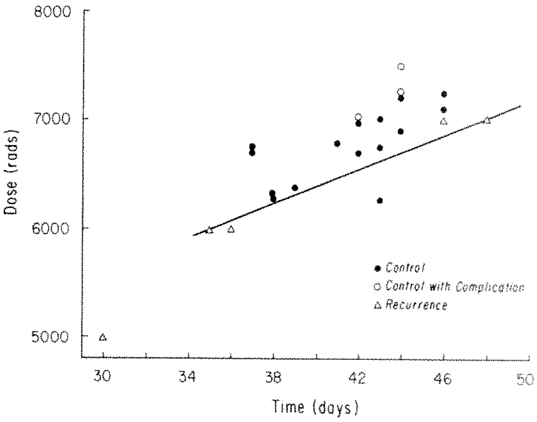

FIG. 2. Time-dose scattergram for 23 head and neck patients treated with twice-a-day fractionation (one patient with a T_x lesion is excluded from the analysis).

TABLE III

CUMULATIVE RECURRENCE RATES IN T_3 AND T_4 SQUAMOUS CELL CARCINOMA OF THE UPPER RESPIRATORY AND DIGESTIVE TRACTS

(Analysis March, 1975)

	No. of Patients	Residual	6 Mo.	12 Mo.	24 Mo.
Split course 3,000 rads/3 wk.; 3 wk. rest 4,000 rads/4 wk. Total time 10 wk.*	23 March 1965 to July 1967	5	11 (48 percent)	17 (75 percent)	18 (79 percent)
850 rads for 5 days/wk. for 8 wk. then 1,000–1,500 rads 1–1½ wk. Total dose 7,500–8,000 rads in 9–9½ wk.*	20 Aug. 1968 to Feb. 1970	2	4 (20 percent)	8 (40 percent)	9 (45 percent)
Twice-a-day fractionation; 1,100–1,200 rads/wk., 6,000–7,500 rads in 5–6½ wk.*	19† July 1973 to July 1974	1	2 (11 percent)	4 (21 percent)	4‡ (21 percent)

* Five days-a-week treatment.

† Three patients with T_2 disease, one from T_x and one treated with 5,000 rads/4 wk. eliminated from analysis.

‡ Nine patients alive without primary recurrence less than 2 yr. (Modified from: Fletcher.[5])

Studded and then confluent mucositis developed during the third and fourth weeks of treatment (Fig. 3*C*). A moist desquamation over a 2.5×7 cm area developed in the anterior upper neck at the completion of treatment (Fig. 3*D*). Both the mucosa and skin healed within three weeks of the completion of radiation therapy.

Two months after the completion of irradiation a modified right upper neck dissection was performed. The specimen contained no detectable tumor. This patient is alive and well one year after radiation therapy.

RAPID TREATMENT FOR INFLAMMATORY BREAST CANCER

The modified Baclesse technique used at the M. D. Anderson Hospital since 1954 with megavoltage delivers 6,000 rads in 8 weeks, *i.e.*, 750 rads per week, followed by a boost of 2,000 to 4,000 rads at 1,000 rads per week. Bolus is used for parts of the treatment in order to produce a brisk erythema followed by a dry desquamation. The technique, however, avoids total denudation of all of the skin included in the tangential fields which would require several weeks to heal. Severe skin atrophy and telangiectasia always develop later.

In this protracted technique, it is possible that the rapid growth of tumor cells in inflammatory carcinoma out-strips the regeneration that occurs in the skin, and that, therefore, protraction of the total treatment time in this group of patients might be expected to favor the tumor. The other tissues in the breast are essentially nonproliferative and are not spared by protraction. Therefore, it seemed reasonable to accelerate the treatment schedule to minimize the unfavorable differential between tumor growth and skin regeneration during treatment. This can be achieved by using two fractions per day instead of one, allowing sufficient time between fractions for complete repair of sublethal injury in the proliferating skin epithelium. This halved the over-all treatment time from eight to four weeks. The total dose had to be reduced to compensate for the difference in over-all treatment time.[7] Each tangential field is treated at every session. A boost of 2,000 rads in two weeks to 3,000 rads in three weeks is to follow.

Seventeen patients with inflammatory carcinoma of the breast, manifested clinically by erythema, *peau d'orange*, and wheals or ridges, have been treated with a twice-a-day fractionation. The first seven patients received 5,400 rads in 40 fractions in four weeks. In the first two patients, bolus was used for four fractions. At six weeks, both patients developed a confluent moist desquamation over the breast which took several weeks to heal, therefore delaying delivery of the boost. The next five patients were treated with 5,400 rads and no bolus was used. One patient developed a confluent and the other four an almost

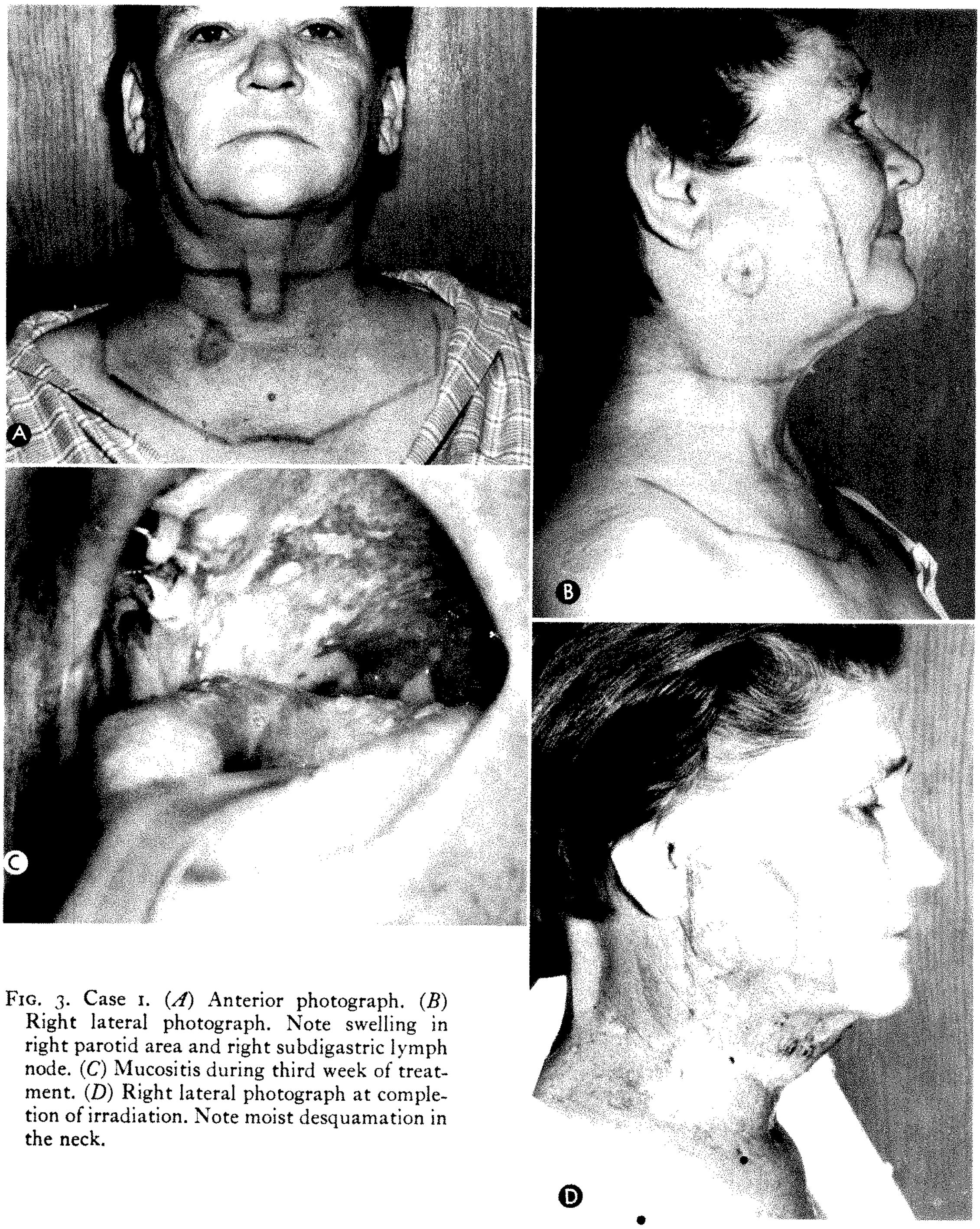

Fig. 3. Case 1. (*A*) Anterior photograph. (*B*) Right lateral photograph. Note swelling in right parotid area and right subdigastric lymph node. (*C*) Mucositis during third week of treatment. (*D*) Right lateral photograph at completion of irradiation. Note moist desquamation in the neck.

TABLE IV

TWICE-A-DAY FRACTIONATION: INFLAMMATORY CARCINOMA OF THE BREAST
April 1972–August 1974
(Analysis March 1975)

	Control in Breast	Survival >1 yr. NED*
	percent	percent
Without chemotherapy	100 (11/11)†	27 (3/11)
With chemotherapy	71 (5/7)	43 (3/7)
Total	89 (16/18)	33 (6/18)

* No evidence of disease.

† Two patients had recurrent disease in the internal mammary area which was not treated twice-a-day and one patient had a metastasis outside the irradiated areas that spread into the breast.

confluent moist desquamation. The dose has been reduced for the last eleven patients to 5,100 rads using no bolus. These patients have had only a brisk erythema and dry desquamation. With this scheme, the weekly rate was 1,300 rads instead of 750 rads as in the eight week treatment. The peripheral lymphatics were treated conventionally. Seven patients with massive disease received various types of multidrug chemotherapy to initiate regression. The most commonly used drugs were methotrexate, 5-fluorouracil, cytoxan, and adriamycin. In several of these patients, a dramatic regression and at times complete clinical disappearance of the disease was obtained.

Local control in the breast has been achieved in 89 percent (16 of 18) of the patients with or without adjuvant chemotherapy (Table IV). All patients with local control survived for more than one year. There is no difference in the control rate in the patients who received 5,400 or 5,100 rads. This control rate compares favorably with a 62 percent control rate obtained in patients previously treated at this institution with conventional fractionation.[2]

Six of the 18 patients are alive without disease for more than one year. Two of these patients have now been followed for over two years.

Three patients have developed a radiation pneumonitis. In most patients, the skin over the breast has telangiectasia and atrophy and there is some fibrosis of the breast. The sequelae, so far, have not been disabling nor even bothersome.

CASE II. A 61 year old white female was seen in September, 1973, with a massive inflammatory carcinoma of the left breast. The area of inflammatory component, consisting of erythema, *peau d'orange*, and ridges, covered the entire breast measuring 20×12 cm (Fig. 4*A*). The patient did not receive chemotherapy prior to irradiation.

The breast was treated with ^{60}Co through tangential fields to 5,100 rads tumor dose in four weeks with twice-a-day fractionation, both fields treated at each session. No bolus was used. The internal mammary, supraclavicular, and axillary areas were treated conventionally with ^{60}Co to 5,000 rads in five weeks plus a boost to palpable axillary lymph nodes. After a two week rest to allow healing of a dry desquamation with a small area of moistness (Fig. 4*B*), a "squeeze boost" of 2,000 rads tumor dose in two weeks (20 fractions) was given also with twice-a-day fractionation to the breast.

The patient is alive and well one and a half years after treatment. The chronic changes in the breast consist of skin atrophy and fibrosis (Fig. 4*C*).

DISCUSSION

HEAD AND NECK

Hyperfractionation has been used in advanced head and neck carcinomas. Acute mucosal reactions and late complications appear to be similar to those observed in conventional treatment, although a thorough assessment of late effects is hampered by the poor survival of patients with late stage disease.

Interestingly, acute skin reactions in the neck were more severe in the twice-a-day hyperfractionation regimen than in the conventional once-a-day irradiation, a phenomenon not observed in the mucosa of the faucial pillar. This may reflect more sensitization in the skin than in the oral mucosa as a result of differences in the cell cycle redistribution. The skin reactions

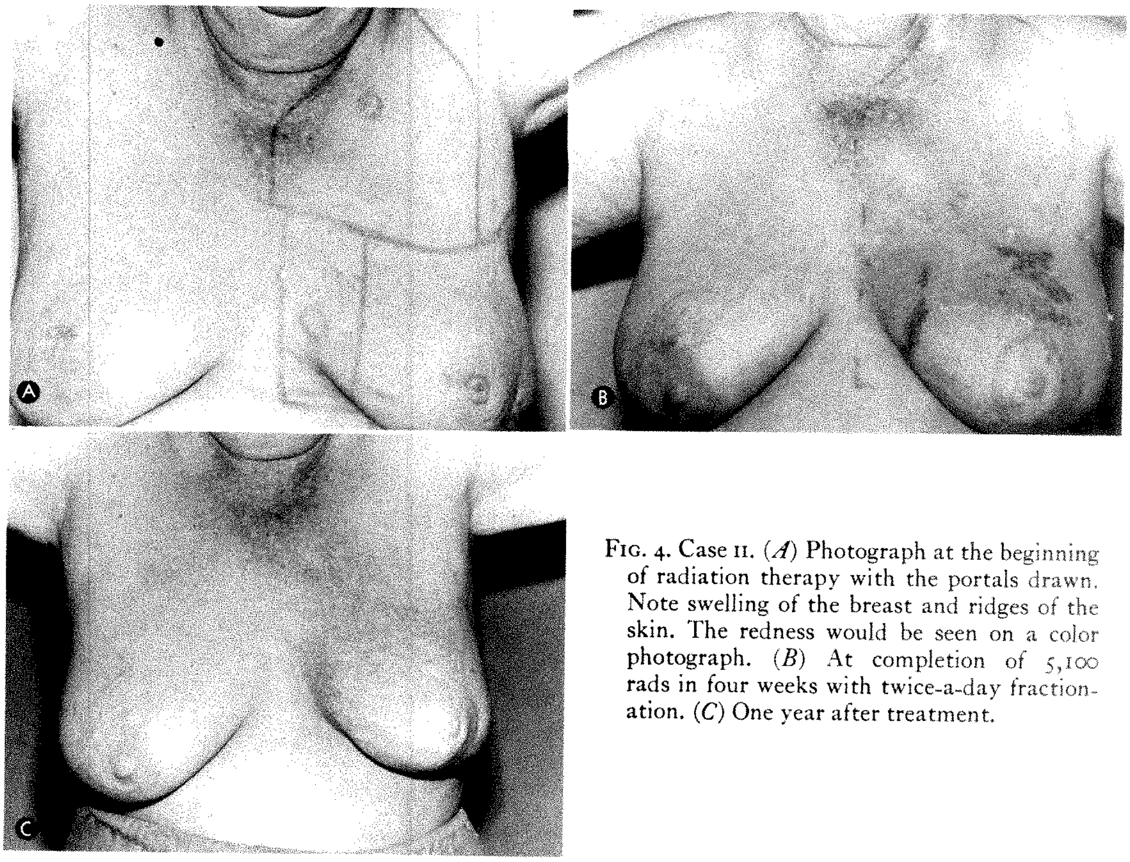

FIG. 4. Case 11. (*A*) Photograph at the beginning of radiation therapy with the portals drawn. Note swelling of the breast and ridges of the skin. The redness would be seen on a color photograph. (*B*) At completion of 5,100 rads in four weeks with twice-a-day fractionation. (*C*) One year after treatment.

healed in a few weeks. The improved local tumor control rate may also reflect a greater effect of redistribution of malignant cells in the cell cycle.

The control rates with twice-a-day fractionation have been increased over those with conventional fractionation, indicating that the therapeutic ratio was improved. Three-times-a-day fractionation has been used by Bäckström *et al.*[1] in 17 head and neck patients with seemingly good results. Comparison with the present series is not feasible since the daily dose rate was 300 rads and, furthermore, most of the patients were operated on. Of four inoperable patients in their series, two were alive and well for over one year.

Although our results are preliminary, they warrant the use of this scheme in patients with earlier disease and in whom distant metastases would not curtail the follow-up.

RAPID TREATMENT OF THE BREAST

The skin reactions in the breast patients were accentuated and required the elimination of bolus as well as reduction of the dose from 6,000 to 5,100 rads. The control rates have been increased over conventional fractionation treatment. An added advantage to this twice-per-day fractionation is the shortening by four weeks of over-all treatment time.

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Vol. 126, No. 1

VOLUME AND TIME FACTORS IN INTERSTITIAL GAMMA-RAY THERAPY*

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ABSTRACT:

The two suppositions which have dictated time-dose and volume relationships in interstitial gamma ray implantation have been examined in the light of recent publications. The first of these assumptions, that total dose reduction is required when the dose rate exceeds 6,000–7,000 rads in seven days, does not appear to be substantiated by clinical experiences. It appears that total dose is the critical treatment parameter and that dose rate may be increased by a factor of two or three without requiring alteration of the total dose.

Although the second classical assumption, "volume increase requires dose decrease," has been shown throughout radiation therapy experience to be generally correct, it should not be applied rigidly to interstitial gamma-ray therapy. In fact, recent experiences seem to indicate that compensation with respect to volume is not an absolute necessity. Larger lesions require, if anything, higher doses than small ones. To obtain a high percentage of controlled, lesions there must be no dose reduction, regardless of increased volume treated.

THE traditional view of time and volume factors in interstitial gamma ray therapy has been clearly expressed by Eric Hall:[15] "The maximum dose that can be delivered without unacceptable damage to the surrounding normal tissue depends, not only on the volume of tissue irradiated, but also on the dose rate, which is in turn a function of the number of radioactive sources used and their geometrical distribution. In order to achieve a consistent biological response, the total dose used should be varied according to the dose rate employed." This concept, which has been uncritically accepted by the radiation therapy community for more than 40 years, was initiated and promulgated by Paterson[25] and has recently been reiterated by Ellis[11] citing the clinical experience of T. A. Green. Ellis did not attempt to quantitate the effect of the volume of tissue irradiated. It is the purpose of this essay to examine the background for their conclusions and to compare this with more recently available information.

BACKGROUND

In 1909, Nogier and Regaud[22] advocated the use of radium to destroy "very radiosensitive cells without, at the same time, causing serious lesions in the general tissues (connective tissue, muscle, blood vessels, etc.)." In 1922, Regaud[32] further stated that the duration of treatment should be prolonged "to a definite limit, so as to make radium therapy of some cancers more efficient without markedly increasing the dose." The implied importance of dose rate is clear. However, in reporting the results of therapy at the Radium Institute of Paris in 1929,[33] the only indication that volume influenced treatment was in the statement that late radionecrosis was seen when extensive lesions (*i.e.*, large volumes)

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were treated by radium implantation. The fault was thought to lie with insufficient filtration of the radioactive sources.

Much of the literature of the three decades following 1908 was devoted to the demonstration of the importance of the time-intensity factor. A summary of the literature by Pack and Quimby[24] in 1932 revealed that: (1) nine authors demonstrated "alterations of time and intensity have no significance in the application of a given dose"; (2) five authors demonstrated "greater effects with less intensity and larger duration of irradiation"; (3) twenty authors demonstrated "greater effects with higher intensity and shorter duration of irradiation"; and (4) four authors demonstrated "greater differential effects on tumor than on normal tissues with longer duration and less intensity of irradiation." These observations were made on a variety of test objects such as experimental animal tumors, normal animal tissues, *Ascaris* and *Drosophila* eggs, bean sprouts, and human skin and ovary. Unfortunately, fundamental problems in interpretation of this material are exemplified by the fact that many of the authors equated fractionation with dose rate and that both roentgen and gamma rays were used in the experiments. In addition, dosimetric practice and the amount and method of filtration for the gamma-ray sources were far from standardized, making interpretation of these early data even more difficult. The influence of volume on dose rate was not explicitly investigated.

It is nearly impossible to separate, retrospectively, the effect of dose rate from that of volume. Indeed, authors did not imply that adjustment should be made to total dose in regard to volume, the number of sources, or the dose rate until Paterson did so in attempting to systematize the interstitial use of radium sources, suitably filtered.

The first of a series of papers by Paterson and Parker[26] presenting a system for the application of radium sources was published in 1934. The subject of dose rate was introduced by the statement " . . . the total dose is the most important single factor in therapy (provided due consideration is given to the duration of radiation.)" In discussion of the biological aspects of radium therapy, he stated that "changes in both malignant and normal tissues as a result of radiation depend not only on total dose but upon the period over which that dose is spread. . . . The dose required to produce lethal change rises as the total period of radiation increases." Since this first paper was chiefly concerned with superficial therapy by mold techniques, tolerance was defined by the skin. The irradiation was to be delivered either continuously or for a period of twelve hours out of every 24. All total doses were to be delivered in a period of seven to ten days. This doubling of the dose rate by treating continuously for twelve instead of 24 hours was not considered deleterious, since the over-all time was not reduced (Table 1).

In 1934, Paterson and Parker[26] commented that a relationship existed between the size of the area irradiated and the degree of reaction. However, they added, "as far as present evidence goes this does not appear to be a very important factor."

With respect to malignant tumors, 6,000 r delivered to the majority of epitheliomas and surrounding normal tissues were said to result in permanent resolution of the tumor with healing of the normal tissues. Although other neoplasms were discussed, the dose suggestions were not so specific, nor were any comments as to volume made.

In 1936, McWhirter[23] published the results of human skin experiments where total dose and over-all time (and therefore daily dose) were constant and the dose rates were varied by factors up to 106 without evidence of change in either acute or late reactions of the irradiated tumor or skin.

Also in 1936, Paterson *et al.*[27] introduced a system of dosage for volume interstitial implantation, and in 1938[28] the rules were further amplified and some clinical observations were made concerning the "limiting tolerance of tissue." The assumption was made "from general knowledge of radiation effects" that tolerance varied with over-all time. The time was therefore taken as seven to ten days, "following the teaching of the Paris school," of continuous implantation. The range of tolerance under these circumstances in "ordinary regions" was taken to be 5,500–7,000 r. "It would seem that the smaller the implanted volume the greater the tolerance."

With the latter stricture in mind, 7,000 r or preferably 6,500 r were said to be "quite safe" for a single plane implant of the tongue, but for large volume implants the suggested limits were 5,500 r to at most 6,500 r. Necrosis was to be expected "in a percentage" of large implants giving doses of 7,500–8,000 r. For large soft tissue implants of neck or axilla, 6,000 r were tolerable.

Considering the practical application of the rules, linear intensities of 1 mg or 0.66 mg of radium per cm could be used for single plane or small volume implants, but for larger volumes, needles of lesser linear intensity were required. If such needles were not available, the duration of the implantation should then be reduced. No quantitative guidelines were offered by which the duration of the implant (total dose) was to be adjusted to compensate for the increase of the dose rate due to the higher intensity sources or for the magnitude of the volume implanted.

In 1948, Jolles[17] published a table of "relative effective dose levels for volumes of different sizes." It was assumed that a dose of 6,000 r over one week in a volume of 75 cc with strict Paterson and Parker distribution was "adequate." The cube root of the quotient of the shell area divided by the volume gave a factor by which the standard dose could be modified. Although there is some discrepancy in the relation of factor to relative dose, the range is from 8,000 r for a volume of 6.23 cc to 5,500 r for 196 cc. No clinical data were given to support the validity of these calculations.

In 1952, in "Studies of optimum dosage," Paterson[29] addressed the problems of dose, time, and volume directly. The conviction was expressed that since "volume increase forces dose decrease," the optimum volume was to be found "near the smallest volume which can reasonably be expected to do the job at all. . . . " An example of tongue and mouth implants was given for three time periods in which a dramatic improvement was seen when the volume irradiated was minimized, "even at some risk of geographic miss."

On the basis of clinical experience acquired in the 1930's, a table of maximum tolerance levels was constructed for radium implants (Table II). A graph was presented (Fig. 1) which was said to represent doses equivalent in five to ten days to any seven day dose chosen. The seven day dose was represented as 100 percent. This graph indi-

Table I*

DOSE RATES WITH CONTINUOUS OR INTERMITTENT RADIUM THERAPY TO ACHIEVE SIMILAR RESULTS WITH SAME OVER-ALL TIME AND SAME TOTAL DOSE

Continuous Dose Rate/hour	Intermittent Dose Rate/hour 12 hours out of 24 hours	Total Time in Hours	Total	
15.6	31.2	192	3,000	Faint erythema
23.4	46.8	192	4,500	Definite erythema
31.3	62.6	192	6,000	Moist desquamation
39.0	78.0	192	7,500	Borderline for skin safety
46.8	93.6	192	9,000	Severe reaction with definite percentage of permanent necrosis

* Adapted from Paterson, R. and Parker, H. M., *Brit. J. Radiol.*, 1934, 7, 592–632.[26]

Table II*

Type	Size in cc	Average Dose in 7 Days in r
Single plane	10 (1 cm slab)	7,500
Small volume	30 cylinder	7,000
Large volume	60 cylinder	6,500
Volume	70 cylinder	6,000
Single plane	200 (1 cm slab)	5,500
Large single plane	300 (1 cm slab)	5,000

* Adapted from Paterson, R., *Brit. J. Radiol.*, 1952, *25*, 505–516.[29]

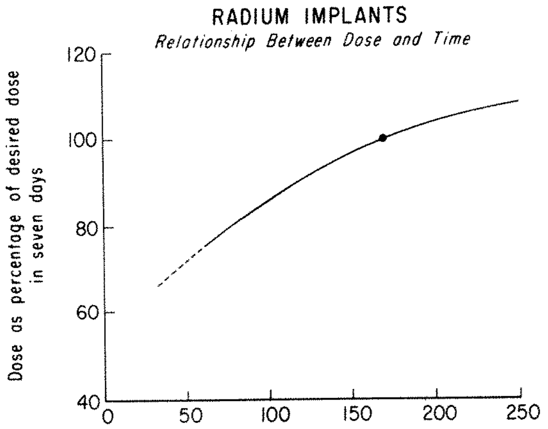
cated that the slope of biological equivalence was much steeper for implant durations less than 150 hours and much flatter for durations above this point.

In this paper, Paterson stated that the "usual practice for years has been a median dose of about 7,000 r in seven days, with 7,500 r for smaller growths and 6,000 to 6,500 r for larger ones. . . . " It was his opinion that these levels were in excess of the "optimum" dose and that, in the future, lesser doses of about 6,000 r should be used. It was acknowledged that, "In its original form it (Fig. 1) perhaps owed more to inspiration than to science, but it has gradually been corrected to match actual experience and seems now to be fairly close to the truth." Paterson has never published quantitative clinical data, in either tabular or graphic form, to substantiate this statement.

In 1968, Ellis[11] stated that the reaction to a dose of 6,000 rads in seven days was a "standard tolerable condition." "The same dose given in a shorter time will produce a greater reaction than this." An isoeffect curve was produced showing the dose and time required to effect the same biologic reaction as 6,000 rads in seven days over a range of one to eleven days. The shape of the curve was determined by clinical data from T. A. Green, data which incidentally have not been published by either Green or Ellis. The calculations, in 1961, by Lajtha and Oliver[19] of relative total doses of continuous irradiation to produce the same effect as various acute single doses of roentgen rays were said to be "in fair quantitative agreement with the observations on protracted treatments obtained from clinical experience (Dr. [T.] A. Green, Royal Northern Hospital, personal communication).

Prior to this time, between 1952 and 1963, Paterson had found the optimum (100 percent) dose to be 6,000 rads in seven days rather than 7,000 r in seven days. When the curves of Ellis and Paterson are plotted together, as done by Hall[13] (Fig. 2), there is a substantial agreement between the two. Unfortunately, since neither curve has been corroborated by quantitative clinical data, this agreement cannot be assumed to represent remarkable similarity of results reached independently by two independent investigators.

In discussing the volume effect, Ellis[11] states " . . . it is clear that, to achieve the maximal tumor effect, the NSD (connective tissue tolerance) must be reached not by reducing total dose, as compared with treating a smaller volume. It can be seen therefore, that no specific volume correction is necessary when this principle is applied."



From: Paterson, R., Brit. J. Radiol., 25, 505, 1952.

Fig. 1. Isoeffect curve for continuous low dosage irradiation. The curve given in the second edition, 1963, differs slightly from this one. (From Paterson, R., *Brit. J. Radiol.*, 1952 *25*, 505.[29])

DISCUSSION

Extensive clinical experience has demonstrated that interstitial low dose rate gamma-ray therapy is effective. As we have seen, the roles of time and dose factors have been determined by a strictly pragmatic approach, unsupported by data other than anecdotal experience. In order to assess the relationship of dose rate, total dose, and volume, it is necessary to review some of the hypotheses advanced to explain the mechanism of action in low dose rate irradiation.

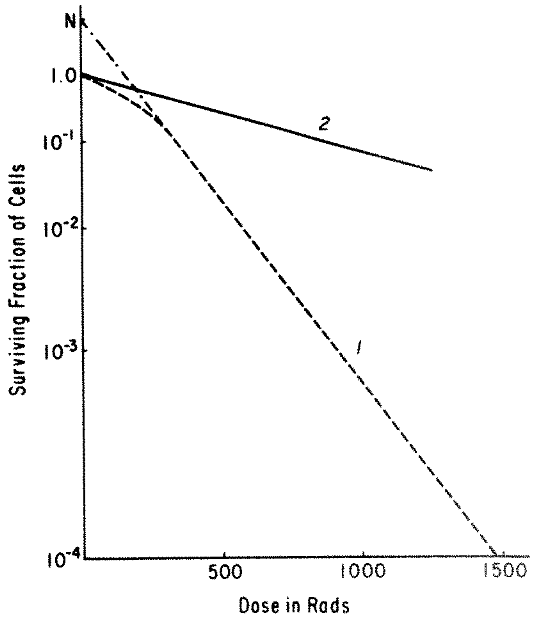
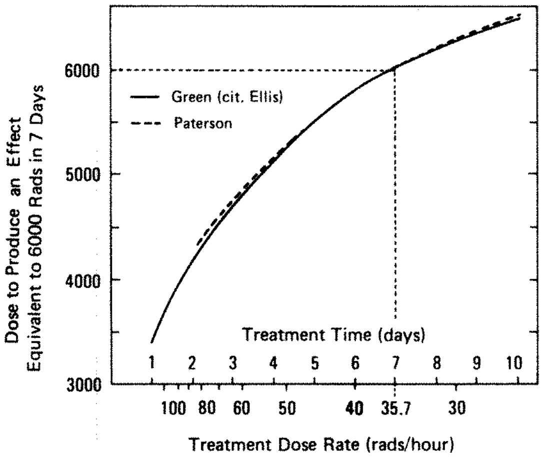


Fig. 3. Theoretical survival curves. 1. Multihit survival curve with extrapolation number, N. 2. Exponential survival curve with slope corresponding to initial slope of curve 1. (Adapted from Barendsen, G. W. In: *Theoretical and Experimental Biophysics*. A. Cole, Editor. Marcel Dekker Inc., New York, 1967.[2])



From: Hall, E. J., Radiology, 102, 173 - 179, 1972.

Fig. 2. Variation of total dose with treatment time to produce an effect equivalent to 6,000 rads in seven days with a radium implant. (Full line from: Green, cited by Ellis, F.: In: *Current Topics in Radiation Research*, North-Holland Publishing Co., 1968, pp. 359–397.[11] Dashed line from: Paterson, R. In: *The Treatment of Malignant Disease by Radiotherapy*. Second edition. Williams & Wilkins, Baltimore, 1963.[25] From: Hall, E. J., *Radiology*, 1972, *102*, 173–179.[14])

Until the development of a simple, rapid method for growing single mammalian cells into macroscopic colonies with high plating efficiencies, bacteria formed the majority of test objects for the plotting of survival curves after acute doses of radiation. Although sigmoid survival curves were reported by Lacassagne and Holweck[18] and Gates,[12] most workers studying the bactericidal action of radiations obtained exponential curves.[20] In 1956, Puck and Marcus[31] established experimentally a characteristic survival curve for mammalian cells exposed to single doses of roentgen rays. When the logarithm of the surviving fraction is plotted against dose, there is an initial shoulder with low doses which becomes straight as the doses increase (Fig. 3, curve 1). The presence of the shoulder was thought to "constitute evidence for a multiple hit killing mechanism" and is taken to represent the range in which sublethal damage is accumulated. In 1960, Elkind and Sutton[10] showed experimentally that when a dose sufficient to reduce the surviving fraction to the exponential portion of the survival curve is divided into two fractions given 30 minutes or more apart, the shoulder is repeated, indicating the rapidity and efficiency of the repair. Multiple equal fractions separated to allow for repair of sublethal damage demonstrate the repetition of the shoulder for each fraction. Since the initial slope of the survival curve is not zero, it may be assumed that cell killing in this region is due to irreversible damage caused by events which do not require the accumulation of sublethal damage, *i.e.*, damage caused by the inactivation of a sensitive target or targets by the deposition of energy resulting from a single particle traversal. Using the cell survival data of Puck and Marcus[31] and the recovery data of Elkind and Sutton,[10] Lajtha and Oliver[19] calculated that the survival curve "for low dose rate is practically a straight line on the logarithm plot with an extrapolation number of one corresponding to that obtained with a single hit process." Support for this calculated single hit curve was experimentally derived from cell survival studies by several investigators[3,4,16] who demonstrated that as the dose rate was lowered, the slope of the survival curve was reduced, the shoulder was eliminated, and the extrapolation number returned to unity (Fig. 3, curve 2).

Barendsen[2] postulated that the exponential type of survival curve seen with low dose rate, low mean linear energy transfer irradiation, is due to irreparable damage produced by single events resulting from the fraction of the total energy deposited at high local energy densities. Burch[6] has calculated that this fraction of the total energy for ^{60}Co gamma rays is in the range of eight to ten percent.

The assumption that the majority of cell killing at low dose rates is of the single traversal variety does not exclude some cell destruction by multihit mechanisms. However, at the clinical dose rate range in use for interstitial gamma-ray irradiation, it is likely that the majority of sublethal damage is repaired during the prolonged course of irradiation. The exception to this may be in cells whose repair capacity is impaired, *e.g.*, by hypoxia,[21] and damage may indeed accumulate producing nonviability in a proportion of cells. Since other mechanisms may be operative, the quantitative estimation of cell killing, when considering single hit events only, is probably underestimated.

Certain limits must be placed on the dose rates under discussion since in conditions of sufficiently rapid proliferation and sufficiently low dose rate, a steady state is achieved. The particular level of dose rate required to achieve the steady state is a function of the type of tissue irradiated. Experimentally, for example, a steady state has developed in rat small intestine at a rate of 16.7 rads hr^{-1},[7] although there is continued depletion of mouse jejunal crypt cells at a rate of 30 rads hr^{-1}.[34] These normal tissues respond to low dose rate continuous irradiation by decreasing the length of their cell cycle. Although a similar phenomenon has not yet been unequivocally demonstrated for malignant cells, there may be a rate so low as to permit proliferation of the tumor in excess of cell killing. At the other end of the scale, it has been shown clinically that increasing the average dose rate by a factor of ten (from 35 to 350 rads hr^{-1}) in continuous irradiation using very high intensity sources (5 mg per cm) produces necrosis in at least 50 percent of cases thus implanted.[9] Increase in dose rate has been shown to effect an increase in cell killing over a wide range, between ten rads hr^{-1} to 100 rads min^{-1}. For the purpose of this discussion, the average interstitial low dose rate range will be taken from 30 to 100 rads hr^{-1} where this effect of dose rate has been shown to be minor.[14]

The assumption that the majority of cell killing in low dose rate therapy is by single traversal events also implies that continous treatment is less affected by changes in cell cycle kinetics. A mathematical model[5] has been presented in which eight parameters, including dose and dose rate per cell cycle, proportion of cells in resistant and sensitive phases of the cell cycle, and the yield of clonogenic cells per cycle can be varied. Comparing low dose rate continuous irradiation with daily fractionated irradiation, there is shown a definite advantage in favor of the continuous strategy if there is a high target number in the resistant phase, if rapid proliferation is present, and if the proportion of time in the sensitive phase is large. This set of parameters is similar to the clinical situation in which interstitial irradiation is often used, *i.e.*, a rapidly growing tumor surrounded by normal tissues which cycle slowly or not at all, *e.g.*, nerve, connective, and vascular tissues.

Clinical evidence at variance with the traditional view of the relation of dose rate to total dose may be found in the evaluation by Awwad *et al.*[1] of 20 patients treated by interstitial radium implantation for squamous cell carcinoma of the oral tongue. In this small group of patients, the total doses administered were corrected for dose rates above 35.7 rads hr^{-1} as recommended in the Manchester system. There was a positive correlation between recurrence and the reduction of the total dose which proved to be of statistical significance.

The experience of Pierquin *et al.*[30] using ^{192}Ir for implantation of 263 patients with squamous cell carcinoma of the skin, oral tongue, floor of mouth, lower lip, and penis is similar. In these patients, the total dose was held constant without regard to the dose rate. Treatment was given to 20 percent of the group in three to four days, 45 percent in five to six days, and 35 percent in seven to eight days, delivering a total dose of 7,000 rads ± five percent. The conclusion was reached that "variation in over-all treatment time for the same tumor dose from three days to eight days does not appear to influence the frequency of recurrence or necrosis. These complications appear if anything to be less frequent for the short treatment times where the daily dose varies between 2,330 and 1,550 rads," *i.e.*, between 97 and 64.8 rads hr^{-1}. Larger volume implants required more sources and therefore received higher dose rates, but no volume corrections were made, nor were they found to be necessary.

A recent review by Delclos and associates[8] of squamous cancer of the tongue and floor of mouth treated by interstitial radium alone or interstitial implant plus external beam therapy indicates that the incidence of complications, both soft tissue necrosis and osteonecrosis, is the same for primary lesions staged T_1, T_2, or T_3. Since the wide range of volumes represented by these three stages are treated with similar or progressively larger doses, these data indicate no need for downward dose adjustment to compensate for the larger volumes.

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LOW ENERGY RADIONUCLIDES FOR PERMANENT INTERSTITIAL IMPLANTATION*

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ABSTRACT:

An analysis of 318 permanent implants was carried out in an attempt to establish the effectiveness of iodine 125 as compared with radon 222 and iridium 192; and to derive dose-response curves for iodine 125.

Analysis of the clinical results obtained with iodine 125 in comparison with radon 222 and iridium 192 in selected anatomical sites demonstrated that iodine 125 has a higher therapeutic ratio than the other two radionuclides.

A tumor control rate of at least 80 percent with iodine 125 implants might be expected after a good geometrical dose distribution, with a planned initial minimum tumor dose of at least 14,000 ± 2,000 rads. Rapid tumor shrinkage ensures a more or less steady or even increased dose rate over a period of several weeks and improves the local tumor control. Tumors with a longer cell cycle are especially susceptible to irradiation with radionuclides of long half-lives.

THE treatment of localized cancer by permanent interstitial implantation, in our experience, is indicated in two categories of patients. The first category consists of patients with relatively small, accessible cancers amenable to the insertion of radionuclides under local anesthesia, usually on an outpatient basis, providing quick and effective local tumor control. The second category consists of patients with intrathoracic or intra-abdominal tumors, still localized, which cannot be removed because of local extension, because of medical problems, or because their removal would cause severe functional disability.

Several considerations enter into the choice of a radionuclide for permanent implantation. Some are practical, such as cost, availability, encapsulation problems, and the like. The most important, however, from the biologic point of view, is the half-life. This determines, together with the total activity, the dose rate and hence not only the treatment time but also the biologic effect. The energy of the radionuclide is also important because it determines the dose distribution and the protection necessary for exposed personnel.

Artificial radionuclides, such as gold 198 and iridium 192, have certain practical advantages when compared with radon 222: they include greater availability, lower cost, and, to a certain degree, easier protection. A major advance, however, has been the development of low energy iodine 125 seeds as a substitute for higher energy radionuclides. They markedly reduce the radiation exposure, and are readily available, leading to a renaissance in the use of permanent implantation in cancer management.[1,2]

The low energy and the low dose rate have raised several difficulties in attempting to establish optimal dose-response relationships because of the multiplicity of biological factors involved in the response of normal and neoplastic tissues.

The purpose of this report is to present dose-response data in normal and neoplastic tissues based on our clinical results obtained after iodine 125 implantation.

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MATERIAL AND METHOD

Three hundred and eighteen patients with cancer of the prostate or lung, or with metastatic disease in lymph nodes of the neck, treated by interstitial implantation during the period 1960 through 1973 were selected for this study. Both epidermoid carcinomas and adenocarcinomas were represented. Three radionuclides were used: radon 222, iridium 192 and iodine 125.

The method of implantation used at Memorial Hospital is based on the uniform distribution of radioactive sources within the tumor volume: the required radioactivity for specific volumes is obtained by multiplying the average of the three perpendicular dimensions of the implanted volume by a constant of proportionality (*K*), which for iodine 125 is 5.[3,4] This method of implantation results in a nonuniform distribution of the dose, the periphery of the implanted tumor receiving about half of the dose given to the center of the tumor. The peripheral dose varies according to the implanted volume, larger doses being given to smaller volumes.[4]

The computerized dosimetry system developed at Memorial Hospital routinely provides isodose contours for each interstitial implant.[5,6] These dosimetric data were reviewed and compared with the configuration and volume of the implanted tumor to obtain the total minimal peripheral tumor dose (TMPD) for each of the iodine 125 study cases. In this report, TMPD denotes the dose delivered to the surface of the implanted tumor by complete decay of the radionuclide, assuming no changes in the size of the implanted volume; a much higher dose than the one specified as TMPD is received by the core of the implant. Figure 1 illustrates the dose distribution for such an iodine 125 implant. In this cross section of a chest, both the primary lung cancer and the hilar lymph nodes were implanted. Although the TMPD is 16,000 rads, the center of the implant has received 32,000 rads.

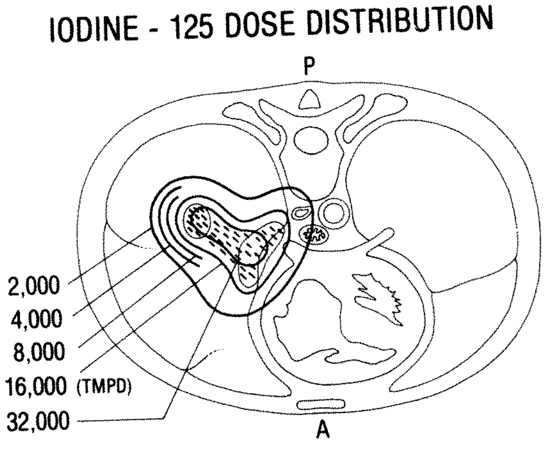

Fig. 1. Iodine 125 implant dose distribution. The total minimum peripheral dose is 16,000 rads but the center of the implanted tumor receives 32,000 rads.

RESULTS

UNRESECTABLE NECK LYMPH NODES

A total of 82 patients with unresectable metastatic epidermoid carcinoma to neck lymph nodes was analyzed in this category. All of these patients had recurrent or persisting cancer after a course of external irradiation (4,000–5,000 rads in four to five weeks). Forty-seven patients were implanted with iodine 125; 23 patients with radon 222; and twelve patients with iridium 192; patients implanted with iridium 192 had, in general, larger tumors.

Table 1 lists the local tumor control and complications according to the radionuclide utilized for implantation. Local control was defined as complete tumor regression with no subsequent local recurrence for four or more months after implantation. The overall tumor control was 67 percent; the tumor control by iodine 125 was 72 percent; by radon 222, 65 percent; and by iridium 192, 58 percent. The late complication rate was 11 percent, 35 percent, and 42 percent, respectively. Late complications in this group included fibrosis, carotid rupture, skin ulcers, and necrosis. Details of the clinical course of these patients have been described elsewhere.[7] Variations in the regression rates were more pronounced in the iodine group than the other two groups.

Figure 2 shows the percentage tumor control *versus* the TMPD obtained by iodine 125 implantation. The vertical bars correspond to two standard deviations (95 percent confidence limits). The horizontal bars indicate the dose range. An 80 percent local control rate was obtained with a TMPD of about 14,000 ± 2,000 rads or more.

Table II shows the relationship of the implanted volume (iodine 125) *vs.* the tumor control and complications. Although the observed differences are not statistically significant ($x^2 = 0.42$), the trend is that the smaller the implanted volume, the higher the local control. No variation was observed in the complication rate and severity of complications according to the volume. Complications in this group included fibrosis (two patients), carotid rupture (one patient) and skin necrosis with ulceration (two patients).

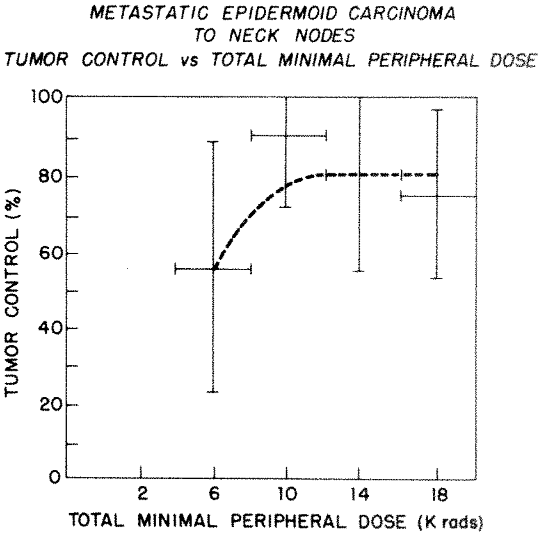

Fig. 2. Percentage tumor control *versus* TMPD obtained by iodine 125 implantation in patients with metastatic epidermoid carcinoma to neck lymph nodes.

The effect of tumor regression rate on local control is shown in Table III. The 47 patients with iodine 125 implants were divided into three groups, according to the median regression time (days required to reach 50 percent tumor volume reduction); again, due to the small samples, the ob-

Table I

METASTATIC EPIDERMOID CARCINOMA; NECK LYMPH NODES: TUMOR CONTROL AND COMPLICATIONS *VS.* RADIONUCLIDES

Radionuclide	No. of Patients	Tumor Control		Late Complications	
		No.	Percent	No.	Percent
Iodine 125	47	34	72	5	11
Radon 222	23	15	65	8	35
Iridium 192	12	7	58	5	42
	82	56	67	18	22

Table II

METASTATIC EPIDERMOID CARCINOMA; NECK LYMPH NODES IMPLANTED WITH ^{125}I: TUMOR CONTROL AND COMPLICATION *VS.* TUMOR VOLUME

Tumor Volume (cm³)	No. of Patients	Tumor Control		Complications	
		No.	Percent	No.	Percent
<10	20	17	85	2	10
11–30	17	11	65	2	12
≥31	10	6	60	1	10
Total	47	34	72	5	11

TABLE III

METASTATIC EPIDERMOID CARCINOMA;
NECK LYMPH NODES:
REGRESSION RATE *vs.* TUMOR CONTROL

Median Regression (in days)	No. of Patients	Tumor Control	
		No.	Percent
⩽ 20	19	16	84
21–40	20	15	75
⩾ 41	8	3	38

served differences are not statistically significant but the trend indicates that the shorter the median regression time, the higher the local control.

UNRESECTABLE CANCER OF THE LUNG

A total of 153 patients with epidermoid carcinoma and adenocarcinoma was studied in this category. Iodine 125 was used for 59 patients, radon 222 for 49, iridium 192 for 45. Local control in this group of patients was defined as complete regression of the implanted tumor as seen on serial chest roentgenograms, with no evidence of recurrence after a four month follow-up period or later. The over-all tumor control rate is 54 percent (Table IV). The tumor control by iodine 125 is 68 percent; by radon 222, 43 percent; and by iridium 192, 49 percent. The complication rate is 2 percent, 22 percent and 20 percent, respectively.

Figure 3 shows the survival rate, calculated by the Berkson-Gage method. The median survival by iodine 125 implantation is eleven months; by radon 222, 8.5 months; and by iridium 192, seven months. The five year survival is 9.6 percent, 3.7 percent and 3.3 percent, respectively.

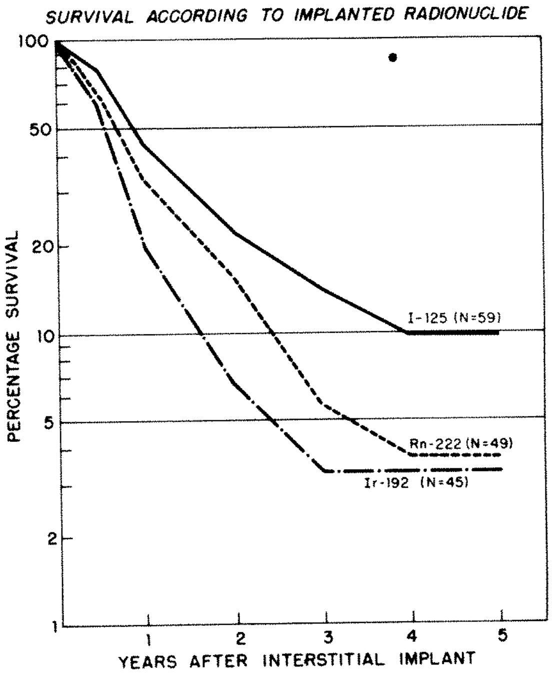

FIG. 3. Percentage survival of patients with unresectable cancer of the lung according to the radionuclide which was used for implantation.

Figure 4 shows the percentage tumor control *vs.* the TMPD for the patients implanted with iodine 125. The vertical bars correspond to the 95 percent confidence limits; the horizontal bars to the dose range. A 70 percent local control rate was obtained with a TMPD of 6,000 rads or more; it should be clarified, however, that

TABLE IV

CARCINOMA OF THE LUNG:
TUMOR CONTROL AND COMPLICATIONS *vs.* RADIONUCLIDES

Radionuclide	No. of Patients	Tumor Control		Complications	
		No.	Percent	No.	Percent
Iodine 125	59	40	68	1	1.7
Radon 222	49	21	43	11	22.0
Iridium 192	45	22	49	9	20.0
	153	83	54	21	14

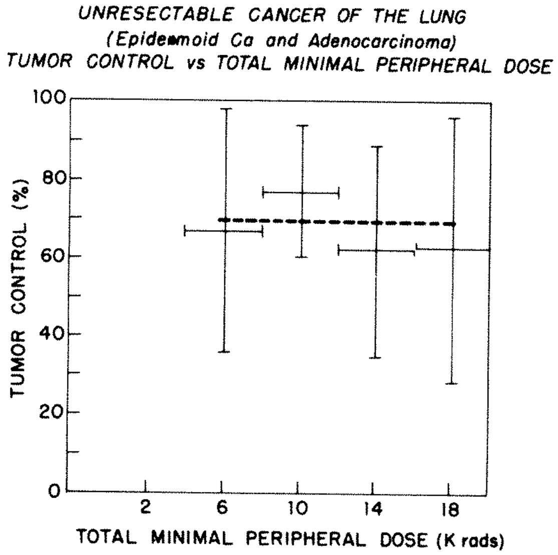

FIG. 4. Percentage tumor control *versus* TMPD for patients with unresectable cancer of the lung implanted with iodine 125.

patients with a TMPD less than 10,000 rads have routinely received supplementary external irradiation (4,000 rads in four weeks with standard fractionation). The minimum effective dose required to obtain a 70 percent tumor control with iodine 125 alone is, therefore, about 14,000 rads.

Table v lists tumor control and complications *vs* the implanted volume for the patients treated by iodine 125 implantation. There is no statistical difference in local control among the three groups.

Figure 5 is an illustrative case of a lung implant in a 59 year old patient with the diagnosis of epidermoid carcinoma of the left upper lobe. A mass measuring 10 cm in its longest dimension was found at thoracotomy in the left upper lobe extending into the mediastinum and involving the main left pulmonary artery and pericardium. The mass was considered unresectable and was implanted with iodine 125 seeds. The TMPD was calculated to be 10,000 rads. Four weeks after implantation, he received a course of external irradiation therapy consisting of 4,000 rads in four weeks (200 rad ×20). Figure 6 shows the same patient eleven months after implantation. Note the marked regression of the

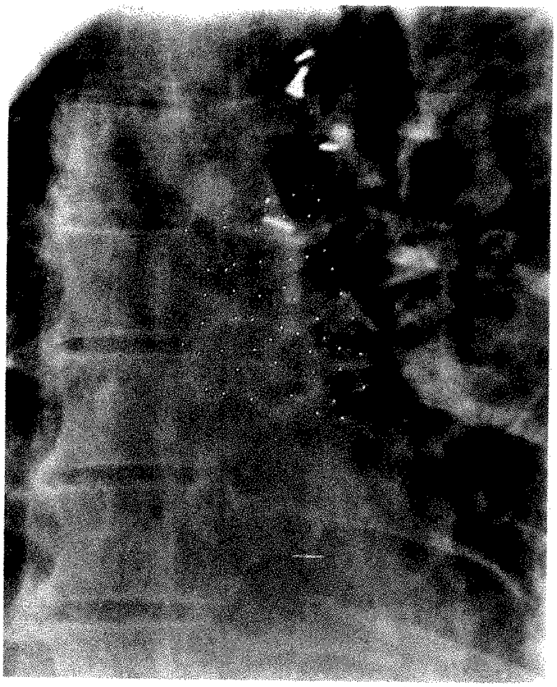

FIG. 5. Example of a 59 year old patient with an unresectable epidermoid carcinoma of the left upper lobe implanted with iodine 125.

TABLE V

CARCINOMA OF THE LUNG; IODINE 125 IMPLANTS: TUMOR CONTROL AND COMPLICATIONS *vs.* TUMOR VOLUME

Tumor Volume (cm^3)	No. of Patients	Tumor Control		Complications	
		No.	Percent	No.	Percent
Less than 10	3	2	67	0	0
11–30	8	5	63	0	0
More than 31	48	33	69	1	2

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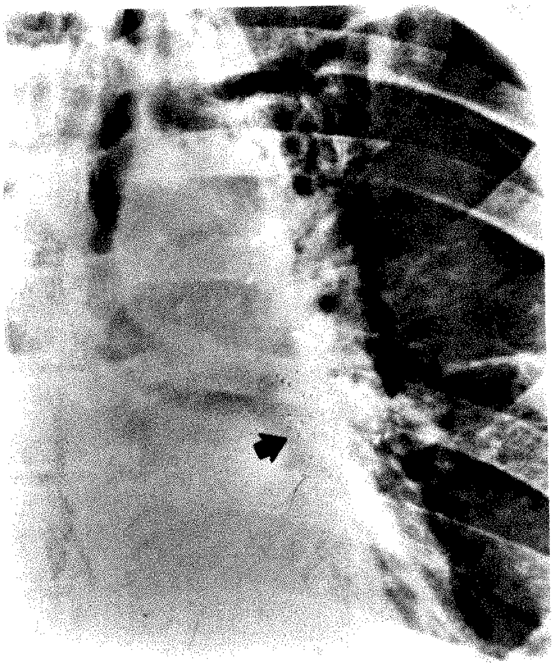

Fig. 6. Roentgenogram of the same patient taken eleven months after implantation. Note the space between the radioactive seeds is markedly decreased, indicating tumor regression.

tumor; the spacing between the radioactive seeds is markedly decreased. This patient is alive and well at this time, six years after implantation.

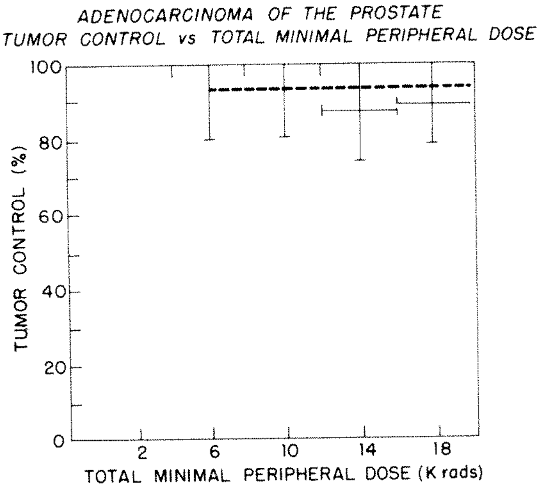

Fig. 7. Percentage tumor control *versus* TMPD of patients with adenocarcinoma of the prostate implanted with iodine 125.

LOCALIZED CANCER OF THE PROSTATE

A total of 83 patients with clinical Stage B and C adenocarcinoma of the prostate was studied in this category. All of these patients were implanted with iodine 125. Local control was defined in this group of patients as complete regression of the palpable prostatic nodule as determined by rectal examination, with no further evidence of recurrence during a follow-up period between 18 and 60 months. Local failures were defined as nodular or diffuse induration persisting or reappearing during the same period of follow-up.

Figure 7 shows the percentage tumor control *vs.* the TMPD. The response curve is similar to the ones observed in the previously discussed sites, but higher. Because the entire prostatic gland is implanted in this site (Fig. 8), the TMPD represents the minimum dose at the surface of the gland, identifiable on roentgenograms by surgical clips positioned on the prostatic capsule at the time of implantation. The minimum tumor dose (dose around the prostatic malignant nodule) in these patients is about 16,000 rads.

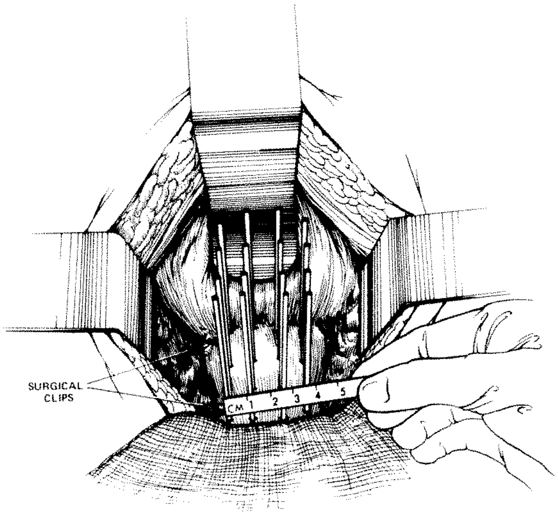

Fig. 8. Schematic drawing of implant of prostate using iodine 125 sources. The entire gland is implanted. Surgical clips are placed on the prostatic capsule for later identification of the gland on localization roentgenograms.

Table VI

ADENOCARCINOMA OF THE PROSTATE; IODINE 125 IMPLANTS

Tumor Volume* (cm^3)	No. of Patients	Tumor Control		Complications	
		No.	Percent	No.	Percent
≤19	11	11	100	0	0
20–29	16	13	81	0	0
30–39	32	30	94	2	7
≥40	24	23	96	4	17

* Enclosed by the 16,000 rads isodose contour.

Table vi shows the relationship of tumor control and complications *vs.* the volume which received at least 16,000 rads. The differences in local control rates among the various groups are not statistically significant. The only complications were encountered in patients with an implanted volume at least 30 cm.^{3} They consisted of transient proctitis and cystitis, but there were no ulcerations nor fistulae.

DISCUSSION

The distinct physical advantages of iodine 125 have been described previously.[8] Previous analysis has also demonstrated that iodine 125 implants have a higher therapeutic ratio than implants with radon 222 or iridium 192.[7] The apparently better results with iodine 125 were confirmed in the present study.

It has been postulated[7] that the superior results of the low energy iodine 125 seeds as compared with radon 222 and iridium 192 are due either to the low dose rate, the continuous radiation over a long time or a higher radiobiological effectiveness (RBE).

In general, a dose rate of less than ten rads per hour results in minimal cell killing in a proliferating cell system. The initial dose rate for an iodine 125 implant varies according to the TMPD. Even with a TMPD of 16,000 rads, the dose rate is only 7.7 rads per hour; it is difficult to explain the cell killing effect of such a low dose rate. Our recent study[9] has shown that there is an increase in the dose rate concomitant with shrinkage of the implanted tumor volume because the sources approximate each other. We feel that the observed good local control rate, despite relatively low initial dose rates, is due to this phenomenon.

It is interesting to note that the tumor control rate is higher in the adenocarcinoma group than in the epidermoid carcinoma (Fig. 9). The reason for this difference is not apparent. It may be due to the better spatial dose distribution obtained, in general, in patients with adenocarcinoma of the prostate, making up the larger category within the adenocarcinoma group of patients. This higher tumor control rate may also be related to the advantages of continuous low dose rates in tumors with longer cell cycle times, as pointed out by

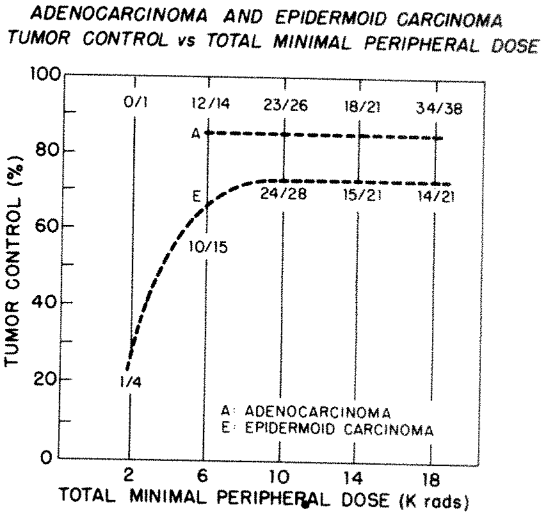

Fig. 9. Tumor control *versus* TMPD for all patients with adenocarcinoma and epidermoid carcinoma.

Lamerton and Courtenay.[7] Studies of cell kinetics of various types of human tumors indicate that adenocarcinomas have a longer cell cycle time as measured by doubling time and labelling index than do epidermoid carcinomas.[11]

Possible gains in RBE can neither be ruled out nor substantiated by the present study. The present clinical data suggest that a tumor which receives a dose below the minimum effective dose of about 14,000 rads and does not regress to 50 percent of the initial size within four to six weeks after implantation will not regress completely. These tumors should receive a supplementary course of external irradiation equivalent to 4,000 rads in four weeks with conventional fractionation; this course of external irradiation, if it is given within six to eight weeks after implantation, will accelerate tumor shrinkage, and thus increase the minimal tumor dose, leading to an improvement in the local tumor control rate.

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GALLIUM-67 SCANS IN CHILDREN WITH SOLID TUMORS*

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ABSTRACT:

Twenty pediatric patients with malignant disease were studied by whole body gallium scans. Seven had Hodgkin's disease, five had soft tissue sarcomas, three had neuroblastomas, two had Wilms' tumors, and one each had a hepatoblastoma, embryonal cell carcinoma, and sacrococcygeal teratoma.

Of 50 sites studied, there was a true positive result in 17 percent, and in 58 percent there were false negative results. The method served best in patients with Hodgkin's disease, where the true positive rate was 64 percent.

In no instance did the gallium scan affect the clinical management of a patient.

GALLIUM 67 as a tumor seeking radionuclide has been widely studied in adults.[4,8,13,15,19,28] Tumors in which total body soft tissue gallium scans have been of value are primarily lymphomas and carcinomas of the lung,[4,7,8,10–12,19,27] but gallium also localizes in sites of inflammation.[4,8,17,20,29] The localization of gallium in rapidly growing tumors and in viable, as opposed to necrotic tissue,[3,8,14,21,26] suggests an active mechanism; but there are many theories, and the true mechanism is unknown.[1,2,5,6,16,25,30]

It has been suggested in the literature[3,8,14,21] that poorly differentiated or undifferentiated malignancies show a greater affinity for gallium than well differentiated lesions. Since childhood malignancies often fall into a less well differentiated type, it was hoped that they might be readily detected by gallium. To date there has been no systematic study in childhood tumors. The present investigation was designed to evaluate the usefulness of gallium 67 scanning in the work-up of pediatric oncological patients.

In almost all of our cases the gallium scan was used not only as a research tool but as a clinical aid in the management of these pediatric patients. This approach limited the accession of patients more than a purely research oriented one would have done, but as scanning is so time consuming and often strenuous on small children, we were not inclined to perform the study unless the clinical situation dictated that it would be of value.

MATERIAL AND METHOD

Twenty patients with malignant disease were studied by whole body gallium scans. They ranged in age from one to 19 years. Fourteen were males, and six were females. Seven children had Hodgkin's disease, five had soft tissue sarcomas, three had neuroblastomas, two had Wilms' tumors, one had hepatoblastoma, one had embryonal cell carcinoma, and one had sacrococcygeal teratoma. All of these children had multiple diagnostic studies including roentgenograms, bone, liver, brain scans, and in some cases, angiography and biopsy. These investigations were used as the basis of comparison to assess the validity of the gallium scan at any particular site. Twenty-two gallium scans were performed, two scans each on the patient with the hepatoblastoma and on a patient with a soft tissue sarcoma in the right iliac fossa.

Gallium 67 was injected intravenously

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Table I

^{67}GA SCANS IN CHILDREN WITH SOLID TUMORS

Pathologic Process (No. of Patients)	No. of Sites	No. of Scans	True +	False −	False +	True −
Hodgkin's Disease (7)	11	7	7	2	1	1
Above diaphragm	6	3	5	0	1	—
Below diaphragm	5	4	2	2	0	1
Soft Tissue Sarcomas (5)	16	6	6	8	1	1
Chest	5	2	3	2	0	—
Abdomen and pelvis	2	2	1	0	0	1
Bone	8	1	2	6	0	—
Liver	1	1	0	0	1	—
Neuroblastoma (3)	15	3	3	12	0	—
Pelvic mass	1	1	1	0	0	—
Abdominal mass	2	1	1	1	0	—
Orbit	1	1	1	0	0	—
Bone lesions	9	2	0	9	0	—
Lymph nodes	1	1	0	1	0	—
Soft tissue mass	1	1	0	1	0	—
Wilms' Tumor (2)	4	2	1	3	0	—
Abdominal mass	2	2	0	2	0	—
Pulmonary metastases	2	1	1	1	0	—
Hepatoblastoma (1)	2	2	0	2	0	—
Pulmonary metastases	2	2	0	2	0	—
Embryonal Cell Carcinoma (1)	1	1	0	1	0	—
Pulmonary metastases	1	1	0	1	0	—
Sacrococcygeal Teratoma (1)	1	1	0	1	0	—
Pelvic mass	1	1	0	1	0	—
Total	50	22	17	29	2	2

in a dosage of 0.035 millicuries per kilogram of body weight. Anterior and posterior scans were obtained at 48 or 72 hours, or both. Scans were done on an Ohio Nuclear Rectilinear scanner with a five to one minification in most cases. All patients were prepared by laxatives to clear the gallium excreted into the colon, and occasionally cleansing enemas were necessary. For small or active children sedation as required was administered orally using chloral hydrate at 50 mg/kilogram body weight to a maximum of 750 mg.

The whole body radiation dose from gallium 67 is reported to be 300 millirads per millicurie injected.[8,24] Therefore, for a ten to 40 kilogram child the total body dose is from 100 to 400 millirads, which is small and acceptable.

RESULTS

The results of all the scans are summarized in Table I. There were 50 sites studied. In 17 of the 50 sites (34 percent), the scans showed a true positive result. In 29 of the 50 sites (58 percent), the study showed a false negative result. Fifteen of the false negatives were in sites of bone metastases. There were only two false positive studies. The two sites listed as "true negatives" represented lack of gallium localization in a site which was thought clinically positive, but was subsequently proved negative.

Seven patients with Hodgkin's disease had gallium 67 scans to evaluate eleven sites. There were seven true positives. Figure 1 shows a urogram of a boy with Hodgkin's in the left para-aortic lymph nodes and in the para-spinal area, and the gallium scan (Fig. 2) was positive in these areas. The two false negatives occurred when gallium failed to localize in involved celiac and para-aortic lymph nodes of two patients with Hodgkin's disease. The single false positive in the Hodgkin's disease group represented gallium uptake in a lymph node containing no tumor, but with reactive hyperplasia and central necrosis. The true negative gallium scan was in a patient with a clinically detected abdominal mass thought to be recurrent Hodgkin's; however, careful evaluation and subsequent long term follow-up was negative.

In five patients with soft tissue sarcomas, six scans were done to evaluate 16 sites. There were six true positives. There were eight false negatives, six of which were in bone. Chest roentgenograms (Fig. 3) of a patient with metastatic undifferentiated sarcoma showed a large left retrocardiac mass, a right hilar mass, and right basal pulmonary metastases all of which were detected on gallium scan (Fig. 4), although a smaller right mid-lung nodule (Fig. 3) did not localize gallium. A bone scan (Fig. 5) and skeletal roentgenograms of a 16 year old boy with small cell sarcoma showed multiple skeletal metastases; however, the

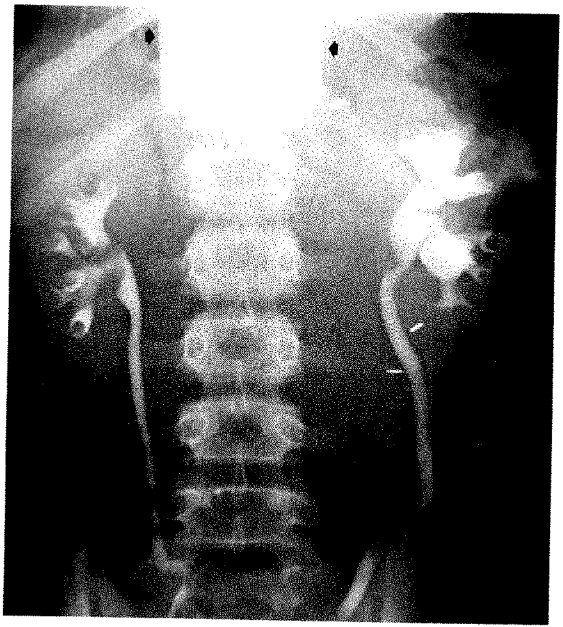

Fig. 1. Film from a urogram of a 13 year old boy with Hodgkin's disease showing a large left retroperitoneal mass displacing the left ureter laterally and a paraspinal mass (arrows) extending superiorly from T-12 and bulging bilaterally.

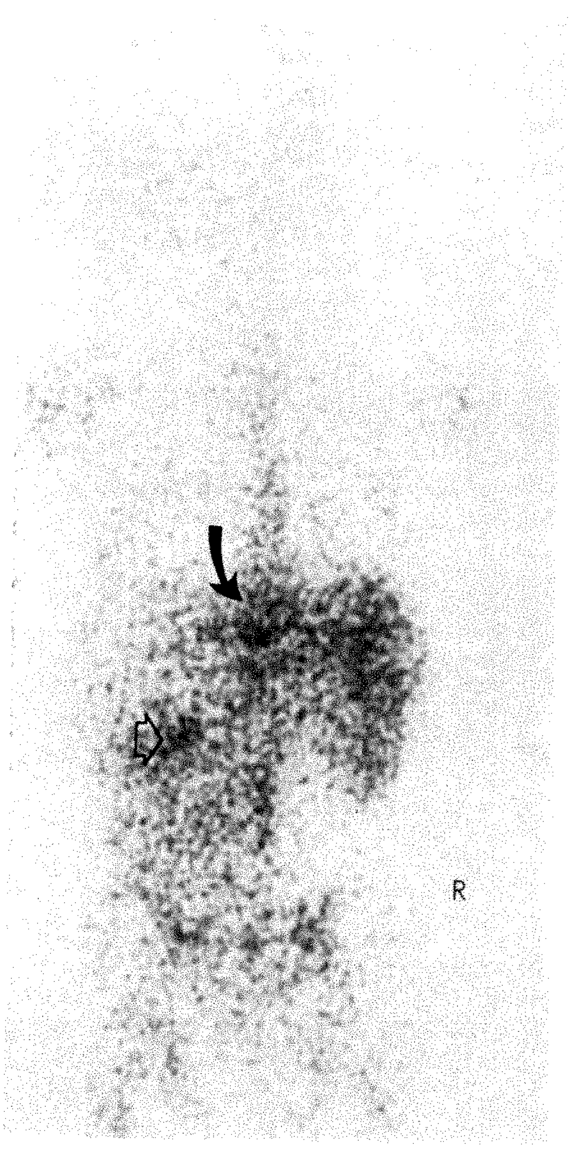

Fig. 2. Posterior Ga-67 scan on a 13 year old boy with Hodgkin's disease showing increased uptake in the left retroperitoneal area (open arrow) and in the T-9 through T-12 paraspinal area (solid arrow). These lesions were demonstrated by roentgenography (Fig. 1).

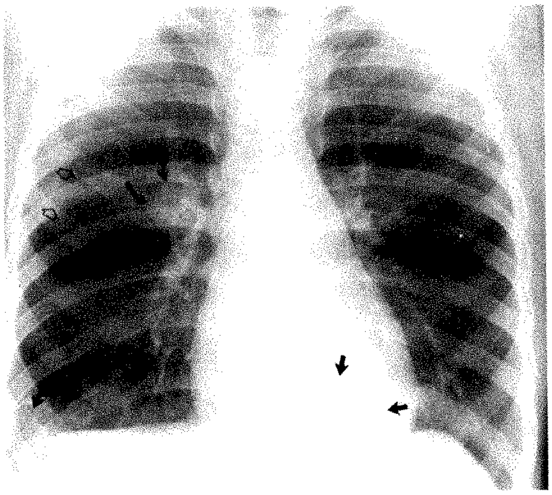

FIG. 3. Chest roentgenogram on a ten year old male with metastatic undifferentiated sarcoma showing a retrocardiac mass (better seen on lateral projection) and right hilar and right basal lung metastasis all identified on Ga-67 scan (Fig. 4). The peripheral $1\frac{1}{2}$ cm right mid-lung nodule (open arrow) was not detected on Ga-67 scan (Fig. 4).

corresponding gallium scan (Fig. 6) must be considered a false negative, showing increased uptake at only two of the multiple sites of bony metastases.

Three patients with neuroblastoma were scanned and 15 sites were studied. Three primary tumors were correctly detected by gallium. There were twelve false negative sites, nine of which were in bone and three of which were in soft tissue. A large left upper quadrant primary tumor was detected (Fig. 7), although an occipital soft tissue mass and multiple bony lesions which were evident on bone scan (Fig. 8) were not detected on the gallium scan.

In the two patients with Wilms' tumor, gallium scans were used to evaluate four sites of which one was a true positive, and three were false negatives. A chest roentgenogram (Fig. 9) showed huge right pulmonary metastases and large left pulmonary metastases. Gallium scan (Fig. 10) in the same patient failed to identify the left pulmonary metastases or a co-existing abdominal mass, although there was gallium localization in the right pulmonary metastases. In the other Wilms' patient a renal arteriogram demonstrated a very large right renal mass, whereas a gallium scan was negative.

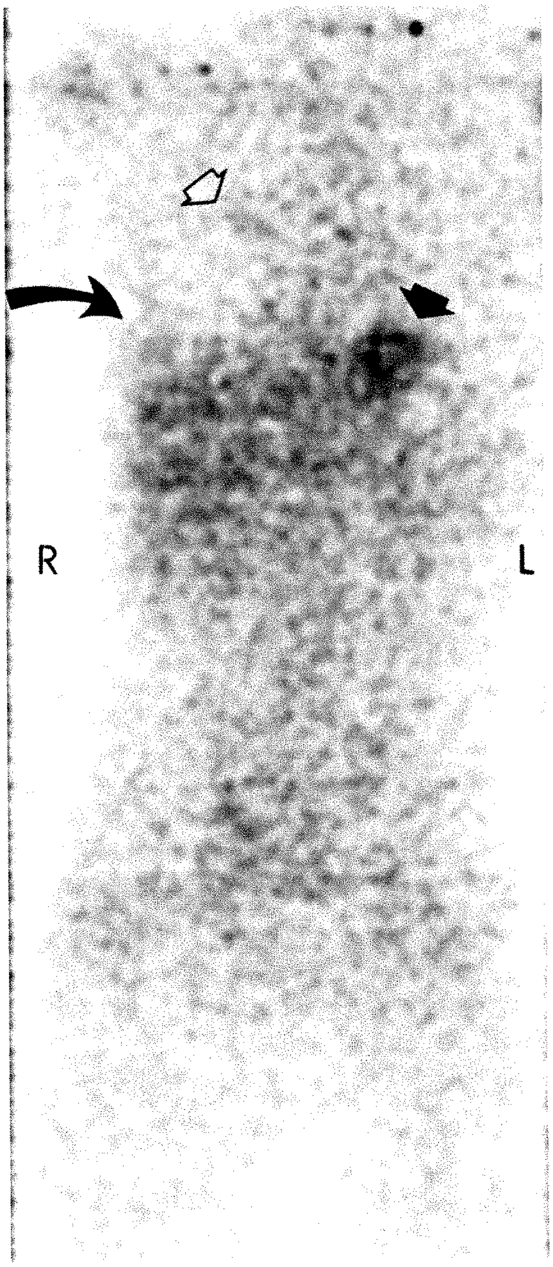

FIG. 4. Posterior Ga-67 scan in a ten year old boy with metastatic undifferentiated sarcoma shows marked increased uptake in the left lung base (retrocardiac) area and moderate increase in the right lung base laterally as well as the right hilum. These correspond to metastases seen on the chest roentgenogram (Fig. 3).

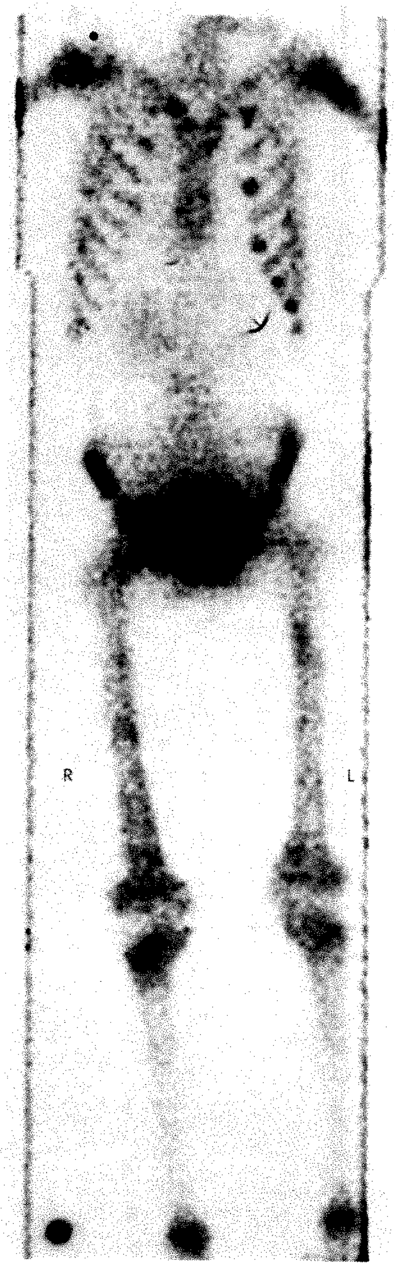

FIG. 5. Anterior technetium 99m diphosphonate scan of the skeleton in a 16 year old male with undifferentiated small cell sarcoma shows unusually high concentration of nuclide throughout the skeleton with focal uptake in the left upper humerus and the cortical regions of both femora. It was felt that the generalized uptake masked other focal sites. Skeletal roentgenograms obtained at the same time showed lytic metastases in both humeri, both scapulae, both clavicles, many ribs, and both femora and proximal tibiae. The entire pelvis was involved with osteolytic metastases.

FIG. 6. Anterior Ga-67 scan on the same subject as in Figure 5 showed only increased uptake in the left shoulder and right pelvis, thereby failing to detect the additional widespread metastatic disease evident on bone scan (Fig. 5) and skeletal roentgenograms.

In three other tumor types gallium scanning gave false negative results at all four sites of evaluation.

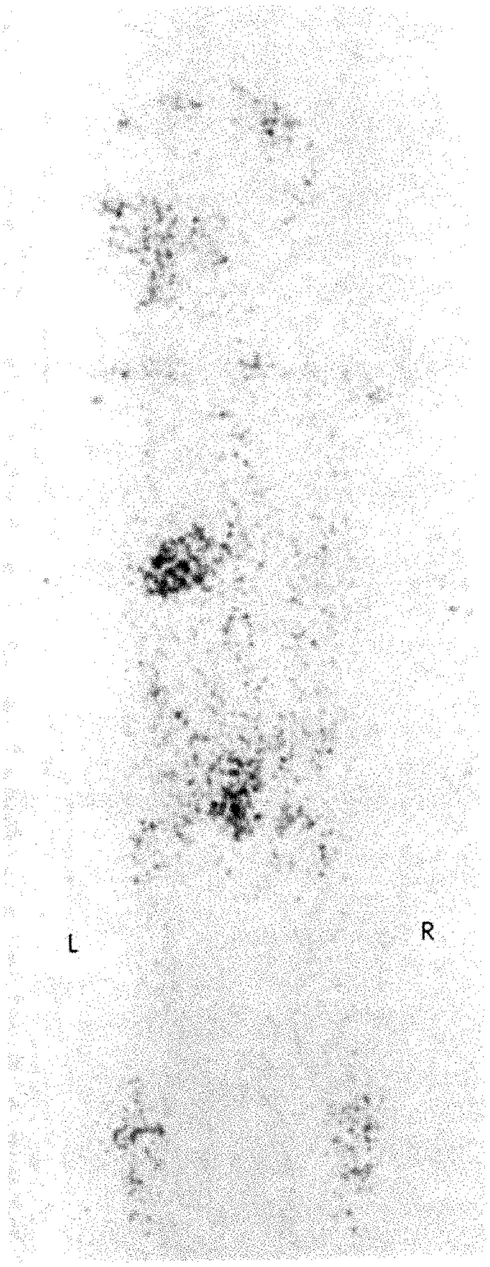

FIG. 7. Posterior Ga-67 scan showing only increased uptake in a left upper quadrant neuroblastoma, while multiple areas of bone metastases (Fig. 8) were not detected.

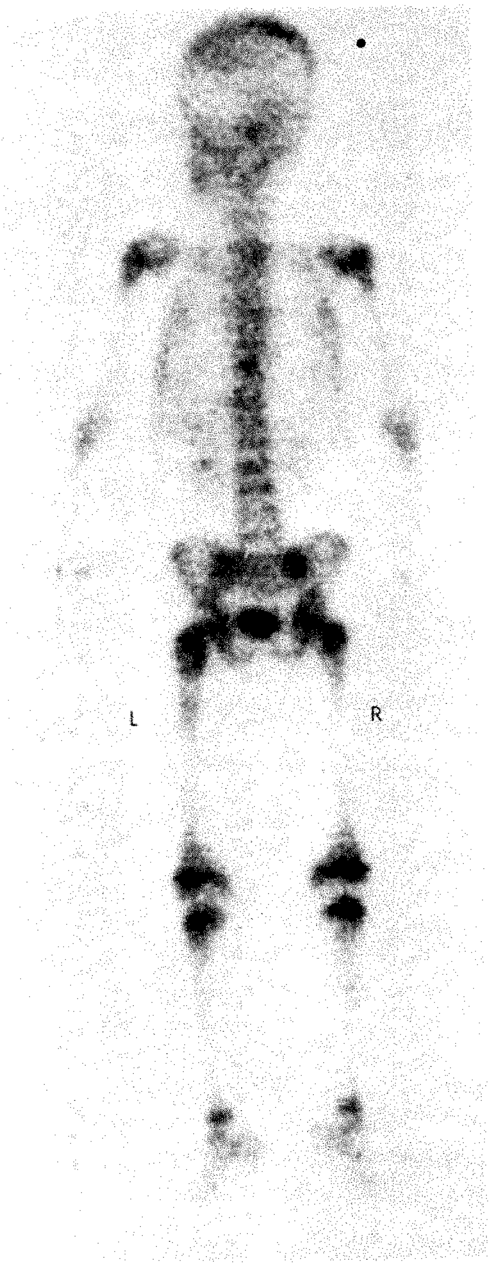

FIG. 8. Posterior Tc 99m polyphosphate bone scan shows metastases to both femora (especially left), the thoracic and lumbar spine, the ribs, and skull in a boy with neuroblastoma.

DISCUSSION

It is evident from our data that gallium 67 scanning was inconsistent as a clinical tool. As expected from adult studies, gallium's greatest accuracy was in cases of Hodgkin's disease, where it showed seven of eleven true positive sites and only two of eleven false negatives. Nevertheless, in only one instance did the gallium scan detect Hodgkin's disease not previously known.

This was the case of a 13 year old girl in whom chest roentgenograms failed to show left peripheral lung nodules later confirmed by tomograms and subsequent biopsy.

Gallium 67 detected soft tissue involvement by sarcomas in four out of eight sites studied, and bone involvement in only two of eight sites studied. However all of these sites of tumor were readily apparent by physical examination or other routine studies. One patient with an unresectable iliac fossa sarcoma had a positive gallium scan initially; however, six weeks after irradiation and combination chemotherapy, a repeat scan was negative. Re-exploratory surgery demonstrated absence of disease thereby confirming the post-therapy gallium scan.

The ability of gallium to detect neuroblastoma was satisfactory for large, clinically obvious primary disease, but not for metastatic lesions. Gallium failed entirely to concentrate in any sites of Wilms' tumor except huge pulmonary metastases. In the three other miscellaneous soft tissue tumors, gallium 67 failed to detect disease.

The failure of gallium to localize in bony metastases in many of our cases differs from results reported by Okuyama *et al.*,[22] but parallels an investigation by Frankel and associates[9] in which technetium polyphosphate bone scans were more accurate than gallium 67 scans in detecting bony metastases. We also concurred with Frankel and associates[9] that lung metastases were poorly detected by gallium when compared to roentgenography. Our results essentially agree with those of Berelowitz *et al.*[4] in Wilms' tumor, where they found no gallium 67 localization in two cases. Littenberg *et al.*[19] used gallium 67 to study three cases of Wilms' tumor and found 66 percent positive correlation with disease. They also had a 50 percent positive correlation with gallium scan in neuroblastoma, which would be roughly equivalent to our find-

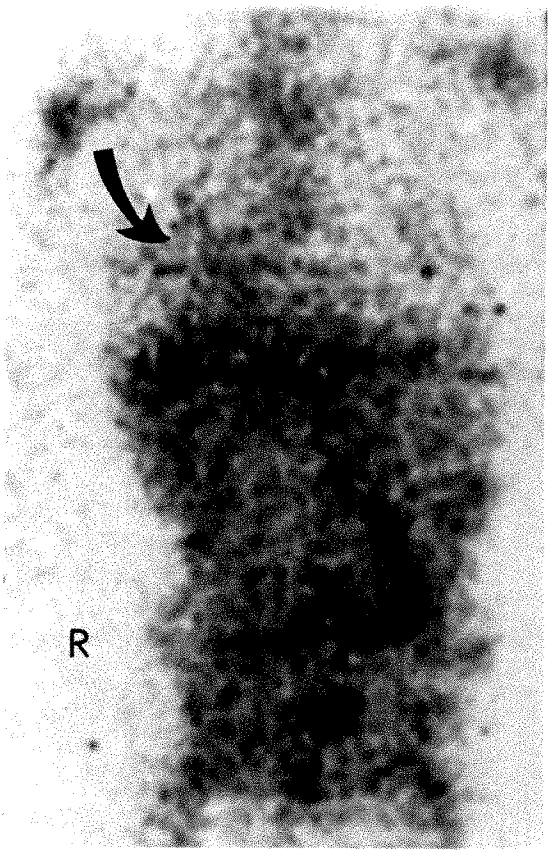

Fig. 10. Anterior Ga-67 scan on a four year old with bilateral lung metastases (Fig. 9) from Wilms' tumor. The scan shows minimal increased uptake in a huge right pulmonary metastases and no uptake in a sizable left lung metastases nor in a co-existing abdominal mass.

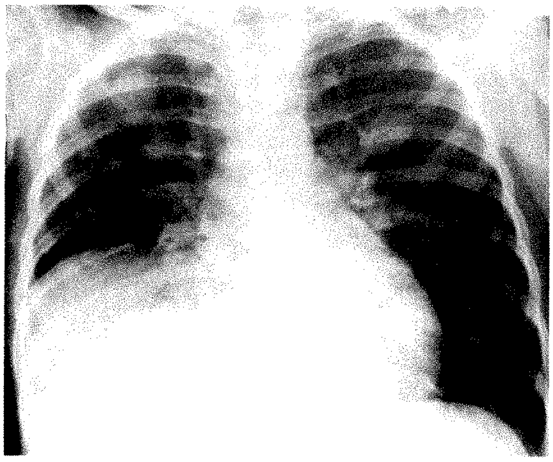

Fig. 9. Chest roentgenogram on a four year old boy showing bilateral pulmonary metastases from Wilms' tumor.

ings in soft tissue sites of neuroblastoma. However, all of our bony lesions of neuroblastoma were false negatives.

The conclusion that we draw from this work is that gallium 67 may still be useful in some cases of Hodgkin's disease, but is of little value in other childhood tumors. In our cases, except for Hodgkin's disease, gallium scanning produced more false negatives than true positives, and in no instance did gallium affect the clinical management of a patient. Therefore we would not recommend its use in clinical pediatric oncology.

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29. VAN DER SCHOOT, J. B. Gallium 67, its tumor affinity and tumor specificity. *Rad. Clin. Biol.*, 1972, *41*, 371–377.
30. WINCHELL, H. S., *et al.* Visualization of tumors in humans using ^{67}Ga-citrate and Anger whole body scanner, scintillation camera and tomographic scanner. *J. Nuclear Med.*, 1970, *11*, 459–466.

THE AMERICAN ROENTGEN RAY SOCIETY

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Representative on the Board of Chancellors and Council of the American College of Radiology: W. B. Seaman.

ANNUAL MEETING: September 20–24, 1976, Washington, D. C., Washington Hilton Hotel.

SCIENTIFIC PROGRAM: Seymour Ochsner, *President Elect*, Ochsner Clinic, New Orleans, La.

MANAGER ANNUAL MEETING: George A. Kling, Harper Hospital, Detroit, Mich.

MEMBERSHIP: Hymer Friedell, Chairman, Executive Council,
Case Western Reserve University, Cleveland, Ohio 44106.

BUSINESS OFFICE: Keith W. Gundlach, Comptroller, American College of Radiology,
20 North Wacker Drive, Chicago, Illinois 60606.

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Representative on the Board of Chancellors of the American College of Radiology: J. A. del Regato.
Liaison Representative on the National Council on Radiation Protection and Measurements: L. Davis.

ANNUAL MEETING: May 9–14, 1976, Vancouver, British Columbia, Bayshore Inn.

SCIENTIFIC PROGRAM: Felix N. Rutledge, *President*, Houston, Texas

LOCAL ARRANGEMENTS: Jay M. Gibson, Vancouver, British Columbia

MEMBERSHIP: Richard H. Jesse, *Secretary*, M. D. Anderson Hospital and Tumor Institute,
Houston, Texas 77025.

BUSINESS OFFICE: Richard H. Jesse, 6723 Bertner Avenue, M.D. Anderson Hospital and Tumor Institute,
Houston, Texas 77025.

EDITORIAL

CHANGING OF THE GUARD

THE guardianship of this JOURNAL, starting as the *American Quarterly of Roentgenology* in 1906, has been continuously entrusted to distinguished editors, not the least of whom is its Editor Emeritus, Traian Leucutia. With wisdom, foresight and dedication, and serving exclusively in a voluntary capacity, he and his predecessors made the JOURNAL an outstanding medical resource. It has provided an authoritative record of many important scientific developments in radiology. Distributed widely throughout the United States and 75 countries abroad, it is one of the leading periodicals in its field. For over 50 of its 70 years the editorship has been located in Detroit. Recently, arrangements have been made to carry on that function in Seattle.

The author of the lead article in this issue and recent Caldwell Lecturer, Ronald Murray, suggested "changing of the guard" to describe this transition. The concept is highly appropriate to the intentions of the Publications Committee and the Editor, namely to guard those qualities that brought the JOURNAL to preeminence. At the same time they conceive of alterations designed to make it more useful and attractive to its international readership.

The revised title, *American Journal of Roentgenology*, in fact the title used from 1913 to 1923, has been chosen to maintain links with the past yet to eliminate strict specification of content. The JOURNAL aspires to include communications of diverse origin and substance that have relevance to radiologic diagnosis and treatment. While maintaining special interest in reports of direct value to clinical practice, it will maintain an alertness for laboratory investigations the results of which would appear to have immediate promise of clinical applicability. The JOURNAL will be receptive to new information irrespective of the sub area of radiology from which it derives. The word roentgenology in the title is intended to relate respectfully to Roentgen but not to exclude any information of significance to the broad field of radiology.

The JOURNAL content will be carefully selected and edited to assure the readership of truth and significance to the full extent contemporary methods and opinions permit. Manuscripts will be reviewed not only by the editors but by peers selected by the Board of Consulting Editors for their special knowledge, competence and interest. Such reviews, often resulting in requirements for revision, will shape the character of the JOURNAL such that authors will come to appreciate it as the preferred outlet for their most important contributions. Quality of content is essential and the new guardians will strive to protect and enhance that crucial feature.

The JOURNAL will also strive to become more contemporary. Segregation of subjects to selected issues will be terminated, as this assures delay for many while providing convenience for only a few. Hopefully each issue will have something of interest to every reader—be it new science, a review of a major problem, recent society or educational meeting news, an editorial opinion or advertising. The educational value of well prepared technical advertising is important to some readers and will be emphasized in its solicitation and selection.

Moreover, the Editorial Office will be constantly alert for means to shorten the periods between receipt of a communication, decision as to its acceptability and its eventual appearance in print. In one interesting study, Roland and Kirkpatrick[1] have shown a surprisingly long period, nearly four years, between conception and publication of scientific medical inquiry. Of this, journal handling and the printing process occupy about 10 months. Currently, the highly contemporary *New England Journal of Medicine* operates with a period of about 160 days between initial receipt of a manuscript, its review, revision if required and publication.[2] The processing time, once a manuscript is accepted is 80 days. For the *American Journal of Roentgenology* the comparable processing time is now 100 days. Both the Editorial Office and Printer will be sensitive to this and although each realizes that introduction of peer review will introduce a delay, each is determined to offset this by accelerating the remainder of the process.

Certain cosmetic changes are already apparent in this issue and others will be forthcoming to make the contents easier to locate, read, index and file. Special attention will be given to maintaining and improving the quality of the illustrations. All aspects of the printer's art will be explored to assure faithful reproduction, but on occasion improved originals from the author may be required to provide the reader with the best possible figures.

The Editorial Office therefore looks upon itself as the servant of the readership, responsible for a useful, attractive and authoritative periodical published with the least possible delay. The cooperation of authors and the advice of readers are essential if the Office is to achieve these goals. Both will be earnestly solicited.

The Journal is entering a period of transition. A new guard takes over, a guard dedicated to maintaining the noble reputation for authenticity of the past yet committed to responding to changes of the future. Radiology has never been static, least of all in these days of proliferating technology and new understandings of human biology and disease. The exciting dynamism of this era challenges this Journal to respond with comparable intelligence and enterprise.

MMT
RHT

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[1] Time lapse between hypotheses and publication in the medical sciences. Roland, C. B., Kirkpatrick, R. A., NEJM 292: 1273-1276, 1975.

[2] Inglefinger, F. Personal communication.

Book Reviewers Needed

The *American Journal of Roentgenology* is compiling a list of prospective book reviewers. Although the journal is unable to provide compensation for such work, reviewers may keep books received as additions to their own libraries. To be considered as a book reviewer, please write AJR's editorial office and indicate your field of special interest.

American Journal of Roentgenology
Room 403 Pacific National Bank Building
4545 15th Avenue N.E.
Seattle, WA 98105

NEWS ITEMS

REFRESHER COURSE IN CARDIAC RADIOLOGY

The North American Society for Cardiac Radiology and co-sponsor, The American College of Radiology, will present the Third Annual Refresher Course in Cardiac Radiology on March 22–25, 1976, in San Francisco, California.

The Course is divided into morning lecture series and afternoon workshops.

This Course is approved for 33 hours of credit for Category 1 of the AMA Physician's Recognition Award and the ACR Continuing Education Credit.

For further information, please write to: Dr. Erik Carlsson, Room M-392, University of California, San Francisco, California, 94143.

WHY AND HOW WE DO SPECIAL PROCEDURES

The Department of Radiology at Mount Sinai Medical Center in collaboration with the Department of Radiology at Jackson Memorial Hospital, University of Miami School of Medicine present the Sixth Annual Postgraduate Seminar "Why and How We Do Special Procedures," March 21–24, 1976, in Miami Beach, Florida.

The Seminar will consist of a total of 20 refresher courses (5 simultaneous courses; each course repeated twice); round table discussions at the end of each day and general sessions. Technical aspects of various vascular and non-vascular special procedures; indications and contraindications; and practical, informal and formal sessions will allow for discussion and exchange of information among registrants and faculty.

This Continuing Medical Education offering meets the criteria for 24 hours of credit in Category 1 for the Physician's Recognition Award of the AMA and mandatory hours for the Florida Medical Association.

For further information, please write to: Mrs. Lucy R. Kelley, Department of Radiology, Jackson Memorial Hospital, Miami, Florida 33136.

WHY AND HOW WE DO CONVENTIONAL RADIOLOGICAL EXAMINATIONS

The University of Miami School of Medicine presents the Fourteenth Annual Postgraduate Seminar in Radiology, "Why and How We Do Conventional Radiological Examinations," on March 24–28, 1976, in Miami Beach, Florida.

Visiting and local faculty will cover the technical aspects (how to do it) of chest, alimentary tract, biliary tract, urinary tract and breast examinations.

This Continuing Medical Education offering meets the criteria for 24 hours of credit in Category 1 for the Physician's Recognition Award of the AMA and mandatory hours for the Florida Medical Association.

For further informations, please write to: Mrs. Lucy R. Kelley, Department of Radiology, Jackson Memorial Hospital, Miami, Florida 33136.

RADIOLOGY 76

The Philadelphia Roentgen Ray Society Bicentennial Program, "Radiology 76," will be held on June 10–12, 1976, in Philadelphia, Pennsylvania.

Distinguished visitors and members of the Philadelphia Roengten Ray Society will discuss current roentgenology, future development trends in Radiology and place in perspective previous progress in the eighty-one-years since Roentgen.

This Continuing Medical Education activity is acceptable for 12 credit hours in Category 1 for the Physician's Recognition Award of the AMA.

For further information, please contact: Peter H. Arger, M.D., Hospital of the University of Pennsylvania, Department of Radiology, 3400 Spruce Street, Philadelphia, Pennsylvania 19104.

GENITOURINARY RADIOLOGY

The New York Medical College, Department of Radiology, will present a postgraduate course "Genitourinary Radiology," on April 5–7, 1976, in New York City.

The distinguished faculty and guest faculty are: Drs. J. A. Becker, W. E. Berdon, J. E. Davis, R. M. Friedenberg, R. F. Girolamo, G. W. Hartman, D. L. King, A. F. Lalli, E. K. Lang, R. M. Lilienfeld, E. T. Longergan, M. A. Meyers, H. M. Pollack, and M. Viamonte.

The course is approved for 18 hours of Category 1 credit.

For further information, please write to: Richard M. Friedenberg, M.D., Department of Radiology, New York Medical College, 1249 Fifth Avenue, New York, New York 10029.

RADIATION ONCOLOGY

The American Cancer Society National Conference on Radiation Oncology, Present Status and Future Potential, will be held on May 27–29, 1976, in San Francisco, California. The conference is held in cooperation with the American Society of Therapeutic Radiologists, Commission on Radiation Therapy of the American College of Radiology and the American Radium Society.

The purpose of this conference is to stress new developments and the contributions that the radiation oncologist can make in the diagnosis and treatment of cancer. Emphasis will be placed on the rationale for selection of therapy and factors influencing the diagnostic and therapeutic usefulness of the newer radiation modalities. A Multidisciplinary "team" approach to the treatment of specific cancer sites will be presented and there will be the opportunity for discussion. The program was planned to provide an opportunity for all physicians to be informed of the increasing value of radiation oncology in the control of cancer.

This Continuing Medical Education offering meets the criteria for 16 hours of credit in Category 1 for the Physician's Recognition Award of the AMA.

For further information, please contact: The Divisions of the American Cancer Society or S. L. Arje, M.D., ACS National Conference on Radiation Oncology, 777 Third Avenue, New York, New York 10017.

CARDIOVASCULAR NUCLEAR MEDICINE: CLINICAL APPLICATIONS

The Second Johns Hopkins Symposium on Cardiovascular Nuclear Medicine will be held on March 11–12, 1976 at the Thomas B. Turner Auditorium, The Johns Hopkins Medical Institutions, Baltimore, Maryland.

Co-sponsors of the symposium are the Council of Cardiovascular Radiology and Clinical Cardiology of the American Heart Association and the Society of Nuclear Medicine.

This second symposium will emphasize recent clinical applications and the use of these procedures in clinical decision making. Demonstrations will be presented to illustrate the technical aspects of the procedures.

The program is approved for 16 credit hours in Category 1 towards the Physician's Recognition Award of the AMA.

For further information, please contact: Program Coordinator, Turner Auditorium, Room 17, 720 Rutland Avenue, Baltimore, Maryland 21205.

BOOK REVIEW

THE ATLAS OF TUMOR RADIOLOGY. Volume 10: The Vertebral Column. By Bernard S. Epstein, M.D. Cloth. Pp. 640, with 280 plates. Price, $40.00. Volume 11: The Accessory Digestive Organs. By Robert E. Wise, M.D., and Austin P. O'Keeffe, M.B., B.Ch. Cloth. Pp. 331, with 302 illustrations. Price, $27.95. Year Book Medical Publishers, Inc., 35 East Wacker Drive, Chicago, Ill. 60601, 1975.

These are the 10th and 11th volumes of the series "The Atlas of Tumor Radiology," sponsored by the American College of Radiology, with the cooperation of the American Cancer Society, the American Roentgen Ray Society, the Cancer Control Program, USPHS, the Eastman Kodak Company, the James Picker Foundation, and the Radiological Society of North America.

Both volumes are excellent. The illustrations are large, clear, and plentiful. With each illustrated lesion there are the clinical story and a narrative description of the roentgen changes.

The volume covering the spine illustrates tumors, benign and malignant, primary and metastatic. In addition, there is extensive coverage of lesions which might be mistaken for tumors: mass lesions, destructive or absorptive processes, granulomas, endocrine disturbances, reticulendothelioses, and abnormalities in the hematopoietic and nervous systems which affect the spine.

The volume on the accessory digestive organs, the pancreas, the liver, gallbladder and their ducts, and the salivary glands presents a considerable portion of its information through angiograms and isotope studies. Ultrasonography is not considered in this volume. Malignant and benign tumors are discussed and illustrated, as well as masses which might be confused with tumors, such as granulomas, cysts, congenital lesions, and parasites.

By design the textual material has been kept to a minimum, as has the bibliographic material. These strictures have more or less distilled, purified, and concentrated that information which is available. Study of these atlases is a quick, simple method of obtaining a vast experience. The volumes are a rapid review of a large amount of sorted, selected clinical material and are a fine refresher course for a mature radiologist; they provide "instant age" for a younger one.

E. FREDERICK LANG, M.D.

BOOKS RECEIVED

THORACIC AND CARDIOVASCULAR SURGERY WITH RELATED PATHOLOGY. Third edition. By William W. L. Glenn, B.S., M.D., F.A.C.S., Charles W. Ohse Professor of Surgery, Yale University School of Medicine; Chief of Cardiothoracic Surgery, Yale-New Haven Hospital, New Haven, Conn.; Averill A. Liebow, B.S., M.D., Professor and Chairman, Department of Pathology, University of California, San Diego School of Medicine; Pathologist-in-Chief, University Hospital, San Diego, Calif.; and Gustaf E. Lindskog, B.S., M.D., F.A.C.S., William H. Carmalt Professor of Surgery Emeritus, Yale University School of Medicine, New Haven, Conn.; with 11 contributors. Cloth. Pp. 1345, with many figures. Price, $55.00. Appleton-Century-Crofts, 292 Madison Ave., New York, N. Y. 10017, 1975.

RADIONUCLIDE DECAY SCHEMES AND NUCLEAR PARAMETERS FOR USE IN RADIATION-DOSE ESTIMATION. By L. T. Dillman and F. C. Von der Lage, Oak Ridge National Laboratory, Oak Ridge Tenn.; and Ohio Wesleyan University, Delaware, Ohio. MIRD Pamphlet. No. 10. Prepared by Medical Internal Radiation Dose Committee of the Society of Nuclear Medicine. Published by the Society of Nuclear Medicine, Inc. Loose leaf binder. Pp. 119. Price, $8.75 with binder, $6.50 without binder. Available from MIRD Committee, 404 Church Avenue, Suite 15 ,Marysville, Tenn. 37801, 1975.

"S," ABSORBED DOSE PER UNIT CUMULATED ACTIVITY FOR SELECTED RADIONUCLIDES AND ORGANS. By W. S. Snyder, M. R. Ford, G. G. Warner, and S. B. Watson, Oak Ridge National Laboratory, Oak Ridge, Tenn. MIRD Pamphlet No. 11. Prepared by Medical Internal Radiation Dose Committee of the Society of Nuclear Medicine. Published by the Society of Nuclear Medicine, Inc. Loose leaf binder. Pp. 257. Price, $10.20 with binder, $7.95 without binder. Available from MIRD Committee, 404 Church Avenue, Suite 15, Marysville, Tenn. 37801, 1975.

SOCIETY PROCEEDINGS

MEETINGS OF RADIOLOGICAL SOCIETIES*

United States of America

American Roentgen Ray Society

Secretary, Dr. James Franklin Martin, 300 S. Hawthorne Rd., Winston-Salem, N. C. 27103. Annual Meeting: Washington Hilton, Washington, D. C., Sept. 20–24, 1976.

American Radium Society

Secretary, Richard H. Jesse, Dept. of Surgery, M. D. Anderson Hosp. and Tumor Institute, Houston, Tex. 77025. Annual Meeting: Bayshore Inn, Vancouver, B. C., Canada, May 9–14, 1976.

Radiological Society of North America

Secretary, Dr. Theodore A. Tristan, Harrisburg, Pennsylvania. Annual Meeting: McCormick Place on the Lake, Chicago, Ill., Nov. 30–Dec. 5, 1975.

American College of Radiology

Executive Director, William C. Stronach, 20 N. Wacker Drive, Chicago, Ill. 60606. Annual meeting.

Section on Radiology, American Medical Association

Secretary, Dr. Antolin Raventos, Davis, Calif. Annual Meeting.

American Board of Radiology

Secretary, Dr. C. Allen Good. Correspondence should be directed to Kahler East, Rochester, Minn. 55901.

Oral examinations will be held: Statler Hilton, Dallas, Texas, Dec. 8–13, 1975; Marriott Motor Hotel, Chicago, Ill., June 14–19, 1976; Sheraton Biltmore, Atlanta, Ga., Dec. 6–11, 1976.

Applications must be received in the Board Office before Sept. 30 of the year preceding the one in which the candidate wishes to be examined.

Deadline for filing applications for any examination in 1976 is September 30, 1975.

American Board of Nuclear Medicine, Inc. A Conjoint Board of the American Boards of Internal Medicine, Pathology and Radiology and sponsored by the Society of Nuclear Medicine.

Application forms and further information are available from the American Board of Nuclear Medicine, 305 E. 45th St., New York, N. Y. 10017.

American Association of Physicists in Medicine

Secretary, Dr. Robert G. Waggener, Dept. Radiol., Univ. Tex. Health Sciences Center, San Antonio, Tex. 78284 Annual Meeting:

American Society of Therapeutic Radiologists

Secretary, Dr. Robert W. Edland, 1836 South Ave., La Crosse, Wis., 54601. Annual Meeting:

American Nuclear Society

Program Chairman, Werner K. Kern, IRD, Space Nuclear Systems, F 309, U. S. Atomic Energy Commission, Washington, D.C. 20545.

American Institute of Ultrasound in Medicine

Secretary, John M. Reid, Ph.D., 556 18th Ave., Seattle, Wash. 98122. Annual Meeting.

American Society of Neuroradiology

Secretary, Arthur E. Rosenbaum, University of Pittsburgh, Pittsburgh, Pa. 15261. Annual Meeting: Peachtree Plaza Hotel, Atlanta, Ga., May 18–22, 1976.

Fourteenth International Congress of Radiology

Rio de Janeiro, Brazil, Oct. 23–29, 1977.

President Elect: Prof. Dr. Nicola C. Caminha; *General Secretary:* Dr. Durval Couto. Av. Churchill, 97-50 and LC-39 20,000 Rio de Janeiro, Brazil.

International Society of Radiology

Hon. Secretary-Treasurer, Prof. W. A. Fuchs, M.D., Department of Diagnostic Radiology, University Hospital, Inselspital, CH-3010 Bern, Switzerland.

Twelfth Inter-American Congress of Radiology

President, Dr. Publio Vargas Pazzos, Casilla 5227, Guayaquil, Ecuador. Meeting in Quito, Ecuador, 1979.

Inter-American College of Radiology

President, Manuel Viamonte, Jr., M.D., Mt. Sinai Medical Center, 4300 Alton Rd., Miami Beach, Fla. 33140.

Secretary, Gaston Morillo, M.D., Jackson Memorial Hosp., 1700 N.W. 10th Ave., Miami, Fla. 33152.

Counselor for the United States, J. A. del Regato, M.D., Univ. of So. Fla. College of Medicine, 13000 No. 30th St., Tampa, Fla. 33612.

Third Congress of the European Association of Radiology

Secretary-General, P.O. Box 14, 79 Lauriston Place, Edinburgh BHI IDB, Scotland.

Second Asian and Oceanian Congress of Radiology

Secretary, Dr. Buenaventura U. V. Angtuaco, Congress Secretariat Headquarters, 2161 Taft Ave., Manila, Philippines. Meeting: Manila, Philippines, Nov. 10–14, 1975.

Alabama Chapter of ACR

Secretary-Treasurer, Dr. Lawrence E. Fetterman, 1720 Springhill Ave., Suite 201, Mobile, Ala. 36604. Meets time and place of Alabama State Medical Association.

Alaska Radiological Society, Chapter ACR

Secretary-Treasurer, Dr. Maurice J. Coyle, 3200 Providence Ave., Anchorage, Alaska 99504.

American Osteopathic College of Radiology

Annual Scientific Meeting: Americana Hotel, Bar Harbor, Fla. Program Administrator: Lawrence J. Jordan, D.O., Suite 21, Ponce American Bldg., 4601 Ponce de Leon Blvd., Coral Gables, Fla. 33146.

American Thermographic Society

Secretary-Treasurer, John Wallace, Ph.D., Dept. Radiol., Thomas Jefferson Univ. Hosp., Philadelphia, Pa. 19107. Annual Meeting.

Arizona Radiological Society, Chapter of ACR

Secretary, Dr. Irwin M. Freundlich, 1501 N. Campbell Ave., Dept. Radiol., Tucson, 85724. Two regular meetings a year. Annual meeting at time and place of State Medical Association and interim meeting six months later.

Ark-La-Tex Radiological Society

Secretary, Dr. Erich K. Lang, Confederate Memorial Medical Center, LSU School of Medicine, Shreveport, La. 71101.

Arkansas Chapter of ACR

Secretary-Treasurer, Dr. Richard Seibold, Jr., Wadley Hosp., Texarkana, Ark.—Tex. 75501. Meets twice annually, the Spring Meeting being in conjunction with and at the place of the State Medical Association.

Association of University Radiologists

Secretary-Treasurer, Dr. Arch W. Templeton, Univ. of Kansas Med. Center, 39th and Rainbow Blvd., Kansas City, Kansas 66103. Annual Meeting.

Atlanta Radiological Society

Secretary-Treasurer, Dr. James H. Larose, Dept. Nuclear Med., South Fulton Hosp., East Point, Ga. 30344. Meets on four Thursday evenings during the academic year at a time announced in early September of each year, at various Atlanta restaurants.

*** Secretaries of societies are requested to send timely information promptly to the Editor.**

Bavarian-American Radiologic Society
Secretary, LTC. Marco J. DiBiase, M.D., Radiology Service, Heidelberg, 130 Station Hosp., APO N. Y. 09102. Meets quarterly.

Blockley Radiological Society
Secretary-Treasurer, Dr. William H. Green, 616 East 24th St., Chester, Pa. 19013.

Bluegrass Radiological Society
Secretary-Treasurer, Dr. Eugene Slusher, Lexington Clinic, 1221 S. Broadway, Lexington, Ky. 40504. The Society meets once each month during the school year.

Bronx Radiological Society, New York State, Chapter ACR
Secretary-Treasurer, Dr. Leon J. Corbin, 1369 Rosendale Ave., Bronx, N. Y. 10472. Meets 4 times a year.

Brooklyn Radiological Society
Secretary-Treasurer, Dr. Ralph Brancaccio, 7901 4th Ave., Brooklyn, N. Y. 11209. Meets first Thursday of each month, October through June.

Buffalo Radiological Society
Secretary, Dr. George J. Alker, Jr., E. J. Meyer Mem. Hosp., Buffalo, N. Y. 14215. Meets second Monday evening each month, October to May inclusive, at University Club.

California Radiation Therapy Association
Secretary-Treasurer, Dr. Duane J. Gillum, Stanford Medical Center, Stanford, Calif. 94304. Meets semiannually in San Francisco and Los Angeles.

California Radiological Society, California Chapter of ACR
Secretary-Treasurer, Dr. John L. Gwinn, 4650 Sunset Blvd., Los Angeles, Calif. 90027.

Catawba Valley Radiological Society
Secretary, Dr. Walter Joe Jacumin, P.O. Box 265, Rutherford College, N. C. 28671. Meets the last Thursday of every month, Holiday Inn, Morganton, N. C. at 7:30 P.M.

Central New York Radiological Society
Secretary-Treasurer, Dr. Alfred Brettner, Auburn Mem. Hosp., Auburn, N. Y. 13021. Meets first Monday each month October through May.

Central Ohio Radiological Society
Secretary-Treasurer, Dr. Daniel E. Lewis, 309 East State St., Columbus, Ohio 43215. Meets second Thursday in October, November, January, March, and May at Fort Hayes Hotel, Columbus, Ohio.

Central Texas Radiology Society
Secretary-Treasurer Dr. E. Jerome Schoolar, Scott and White Clinic, Temple, Tex. 76501. Meets the fourth Monday of each month at Ponderosa Hotel, Temple, Tex. at 7:00 P.M.

Chicago Radiological Society, Division of the Illinois Radiological Society, Chapter of ACR
Secretary-Treasurer, Dr. Harold J. Lasky, 55 E. Washington St., Suite 1735, Chicago, Ill. 60602. Meets third Thursday of each month, October to April, except December, at the Bismark Hotel, Chicago, Ill.

Cleveland Radiological Society
Secretary-Treasurer, Dr. Charles M. Greenwald, 7007 Powers Blvd., X-Ray Dept., Parma, Ohio 44129. Meetings at 7:00 P.M. on fourth Monday of October, November, January, February, March and fifth Monday of April.

Colorado Radiological Society, Chapter of ACR
Secretary, Dr. John Pettigrew, Denver, Colo. Meets third Friday of each month at Denver Athletic Club from September through May.

Connecticut Valley Radiologic Society
Secretary, Dr. Gerald N. LaPierre, 759 Chestnut St., Springfield, Mass. 01107. Meets in April and October.

Dallas-Fort Worth Radiological Society
Secretary-Treasurer, Dr. Robert R. Burns, 1400 Stemmons Ave., Dallas, Tex. 75208. Meets the 3rd Monday of every month at 6:30 P.M., at the Airport Hotel, Arlington, Tex.

Delaware Chapter of ACR
Secretary, Dr. Ekkehard S. Schubert, Wilmington Med. Center, P. O. Box 1951, Wilmington, Del. 19899.

East Bay Radiological Society
Secretary-Treasurer, Dr. Richard H. Culhane, 4 Vista del Mar, Orinda, Calif. 74563. Meets first Thursday each month, Oct. through May, at University Club, Oakland Calif.

East Tennessee Radiological Society
Secretary-Treasurer, Dr. George H. Wood, 205 Medical Arts Bldg., Knoxville, Tenn. 37902. Meets in January and September.

Florida Radiological Society, Chapter of ACR
Secretary. Dr. Paul J. Popovich, 1350 S. Hickory St., Melbourne, Fla. 32901. Meets twice annually, in the spring with the Annual State Society Meeting and in the fall.

Florida West Coast Radiological Society
Secretary-Treasurer, Dr. Herbert Johnson, Davis Blvd., Tampa, Fla. 33606. Meets on 4th Thursday of the months January, March, May, October, and November.

Georgia Radiological Society, Chapter of ACR
Secretary, Dr. E. P. Rasmussen, Piedmont Prof. Bldg., 35 Collier Rd., N.W., Atlanta, Ga. 30309.

Greater Cincinnati Radiological Society
Secretary-Treasurer, Dr. Owen L. Brown, 2421 Auburn Ave., Cincinnati, Ohio 45219.

Greater Kansas City Radiological Society
President-Secretary, Dr. Jay I. Rozen, Suite 216, 6400 Prospect, Kansas City, Mo. 64132. Meets 5 times a year.

Greater Louisville Radiological Society
Secretary-Treasurer, Dr. L. D. LeNeave, 315 E. Broadway, Louisville, Ky. 40202. Meets monthly.

Greater Miami Radiological Society
Secretary, Dr. David C. Hillman, P. O. Box 610544, North Miami, Fla. 33161. Meets monthly, third Wednesday at 8:00 P.M. at various member hospitals, Miami, Fla.

Greater St. Louis Society of Radiologists
Secretary-Treasurer, Dr. Donald Callahan, Northland Med. Bldg., Jennings, Mo. 63136.

Hawaii Radiological Society, Chapter of ACR
Secretary-Treasurer, Dr. Michael J. McCabe, Straub Clinic and Hosp., Honolulu, Hawaii 96813. Meets third Monday of each month at 7:00 P.M.

Health Physics Society
Secretary, Russell F. Cowing, P.O. Box 156, E. Weymouth, Mass. 02189. Annual Meeting.

Houston Radiological Society
Secretary, Dr. Neill B. Longley, 6436 Fannin, Suite 601, Houston, Tex. 77025. Meets fourth Monday of each month, except June, July, August and December, at 6:00 P.M., at 103 Jesse H. Jones Library Building, Texas Medical Center, Houston, Tex. 77025.

Idaho State Radiological Society, Chapter of ACR
Secretary-Treasurer, Dr. John H. Truksa, 1605 Park Ave., Nampa, Id. 83651. Meets in the spring and fall.

Illinois Radiological Society, Inc., Chapter of ACR
Secretary, Dr. Robert D. Dooley, Hinsdale Med. Center, Hinsdale, Ill. 60521. Meets in the spring and fall.

Indiana Roentgen Society, Inc., Chapter of ACR
Secretary, Dr. John A. Knote, Home Hosp., Lafayette, Ind. 47902.

Iowa Radiological Society, Chapter of ACR
Secretary-Treasurer, Dr. Dale L. Roberson, 1948 First Ave., NE, Cedar Rapids, Iowa 52402. Luncheon and business meeting during annual session of Iowa State Medical Society. The scientific session is held in the autumn.

Kansas Radiological Society, Chapter of ACR
Secretary-Treasurer, Dr. Ralph H. Baehr, 310 Medical Arts Bldg., Topeka, Kan. 66604. Meets in spring with State Medical Society and in winter on call.

Kentucky Chapter of ACR
Secretary-Treasurer, Dr. Bernard Sams, St. Joseph In-

firmary, 735 Eastern Parkway, Louisvlle, Ky. 40217. Meets in April and September.

Kings County Radiological Society
Secretary, Dr. Sidney Hendler, 1880 Ocean Ave., Brooklyn 30, N. Y. Meets Kings County Med. Soc. Bldg. monthly on fourth Thursday, October to May, 8:45 P.M.

Knoxville Radiological Society
Secretary, Dr. Clifford L. Walton, Blount Professional Bldg., Knoxville 20, Tenn. Meetings are held the third Monday of every other month at the University of Tennessee Memorial Research Center and Hospital.

Long Island Radiological Society
Secretary, Dr. Harry L. Stein, North Shore Univ. Hosp., 300 Community Dr., Manhasset, N. Y. 11030.

Los Angeles Radiological Society
Secretary, Dr. Arthur F. Schanche, 333 North Prairie Ave., Inglewood, Calif. 90301. Meets second Wednesday of month in September, November, January, April and June at Los Angeles County Medical Association Building, Los Angeles, Calif. Midwinter Radiological Conference. Century Plaza Hotel, Los Angeles, Calif.

Louisiana Radiological Society, Chapter of ACR
Secretary-Treasurer, Dr. Roger H. Tutton, 1514 Jefferson Hwy., New Orleans, La. 70121.

Louisiana-Texas Gulf Coast Radiological Society
Secretary-Treasurer, Dr. J. Gardiner Bourque, 3155 Stagg Dr., Suite 230, Doctors Bldg., Beaumont, Texas 77701.

Maine Radiological Society, Chapter of ACR
Secretary-Treasurer, Dr. Peter E. Giustra, Dept. Radiology, Penobscot Bay Medical Center, Rockland, Maine 04841. Meets in June, September, December and April.

Maryland Radiological Society, Chapter of ACR
Secretary, Dr. David S. O'Brien, Anne Arundel Hosp., Annapolis, Md. 21401.

Massachusetts Radiological Society, Chapter of ACR
Secretary, Di. Joseph T. Ferrucci, Jr., Massachusetts Gen. Hosp., Boston, Mass. 02114.

Memphis Roentgen Society
Secretary-Treasurer, Dr. R. Randolph Ramey, Baptist Memorial Hosp., 899 Madison Ave., Memphis, Tenn. 38146. Meets first Monday Oct. through June at the University Club.

Miami Valley Radiological Society
Secretary, Dr. Bert Must, I.B.M. Bldg., Dayton, Ohio. Meets third Thursday of fall, winter and spring months at 7:30 P.M. at Miami Valley Hospital, Dayton, Ohio.

Michigan Radiological Society, Chapter of ACR
Secretary-Treasurer, Dr. Francis P. Shea, Harper Hospital, 3825 Brush St., Detroit, Mich. 48201. Meets monthly, first Thursday, October through May, at David Whitney House, 1010 Antietam, at 6:30 P.M.

Michigan Society of Therapeutic Radiologists
Secretary-Treasurer, Dr. William I. Knapp, St. Mary's Hosp., 830 S. Jefferson, Saginaw, Mich. 48601. Meets bimonthly during the academic year.

Mid-Hudson Radiological Society
Secretary-Treasurer, Dr. William D. Stiehm, 37 Flower Hill Rd., Poughkeepsie, N. Y. 12603. Meets 7:00 P.M., first Wednesday of each month, September to May.

Milwaukee Roentgen Ray Society
Secretary-Treasurer, Dr. Thomas C. Lipscomb, 1004 North Tenth St., Milwaukee, Wis. 53233. Meets monthly on fourth Monday, October through May, at University Club.

Minnesota Radiological Society, Chapter of ACR
Secretary-Treasurer, Dr. Marvin E. Goldberg, Box 292, Mayo Memorial Health Sciences Center, Minneapolis, Minn. 55455.

Mississippi State Radiological Society, Chapter of ACR
Secretary-Treasurer, Dr. Edward L. Gieger, 969 Lakeland Dr., Jackson, Miss. 39216. Meets third Thursday, excluding summer months, at the Primos Northgate Rest., Jackson at 6:30 P.M.

Missouri Radiological Society, Chapter of ACR
Secretary-Treasurer, Dr. Ronald G. Evens, Mallinckrodt Institute of Radiology, 510 S. Kingshighway, St. Louis, Mo. 63110.

Montana Radiological Society, Chapter of ACR
Secretary, Dr. C. H. Agnew, Room 102, Doctors Bldg., Billings, Mont. 59101.

Nebraska Chapter of ACR
Secretary-Treasurer, Dr. Robert Bodmer, Suite 622 Doctors Bdg., Omaha, Neb. 68131. Meets the third Wednesday of the month, Oct. through March, at the Clarkson Hosp., Omaha, Neb. and the fourth Friday of April at the Lincoln Country Club, Lincoln, Neb.

Nevada Radiological Society, Chapter of ACR
Secretary, Dr. Charles F. Veverka, Carson Tahoe Hosp., Carson City, Nev. 89701.

N.E. Society for Radiation Oncology
Secretary, Dr. C. C. Wang, Mass. Gen. Hosp., Boston, Mass. 02114.

New England Roentgen Ray Society
Secretary, Dr. Melvin E. Clouse, 185 Pilgrim Rd., Boston, Mass. 02115. Meets the third Friday of Oct. and Nov., and third Thurs. of each month. Jan. through May, excluding December, at The Longwood Towers, 20 Chapel Street, Brookline, Mass. at 3:00 P.M. Annual Meeting: May 20, 1976.

New Hampshire Roentgen Ray Society, Chapter of ACR
Secretary-Treasurer, Dr. Edward P. Kane, Claremont Gen. Hosp., Claremont, N. H. 03743. Meets four to six times yearly.

New Mexico Society of Radiologists, Chapter of ACR
Secretary, Dr. W. M. Jordan, 1100 Central Ave. S.E., Albuquerque, N. M. 87106. Four meetings annually, three held in Albuquerque, N. M., and one held at time and place of New Mexico State Medical Society annual meeting.

New Orleans Radiological Society, Inc.
Secretary-Treasurer, Dr. Jimmy L. Mains, P.O. Box 446, Gretna, La. 70053. Meets bimonthly at local restaurants selected by the President. Spring Conference.

New York Roentgen Society
Secretary-Treasurer, Dr. Thomas C. Beneventano, 111 East 210th St., Bronx, N. Y. 10467. Meets monthly on the 3rd Monday at the New York Academy of Medicine at 4:30 P.M. Annual Spring Conference, Waldorf-Astoria Hotel, New York, N. Y., April 22–24, 1976. A.M.A. Cat. I credit. Further information may be obtained from Dr. Albert A. Dunn, Roosevelt Hosp., New York, N. Y. 10019.

New York State Chapter of ACR
Secretary-Treasurer, Dr. Albert F. Keegan, 6 Secor Dr., Port Wash., N. Y. 11050.

North American Society of Cardiac Radiology
Secretary-Treasurer, Dr. Erik Carlson, Univ. Calif., San Francisco, Calif. 94143.

North Carolina Chapter of ACR
Secretary-Treasurer, Dr. Ernest B. Spangler, Wesley Long Hosp., Greensboro, N. C. 27402. Meets twice a year. The Spring Meeting is held at the time of the meeting of the North Carolina Medical Society. The Fall Meeting is held in November at the Mid Pines Club, Southern Pines, N.C.

North Dakota Radiological Society, Chapter of ACR
Secretary, Dr. Marshall Landa, P. O. Box 6001, Fargo, N. D. 58102. Meets at time of State Medical Association meeting. Other meetings arranged on call of the President.

North Florida Radiological Society
Secretary, Dr. David F. Bew, University Hospital of

Jacksonville, 655 W. Eighth Street, P.O. Box 2751, Jacksonville, Fla. 32203. Meets quarterly in March, June, September and December.

Northeastern Oklahoma Radiological Society
Secretary-Treasurer, Dr. Theodore J. Brickner, Jr., 5919 S. Gary Place, Tulsa, Okla. 74110.

Northeastern New York Radiological Society
Secretary, Dr. Donald R. Morton, Dept. of Radiology, St. Clare's Hosp., Schenectady, N. Y. 12304. Meets in Albany area on third Wednesday of October, November, March, April, and May.

Northern California Radiation Therapy Association
Secretary-Treasurer, Dr. John D. Earle, Stanford Medical Center, Stanford, Calif. 94304. Meets quarterly.

Northern California Radiological Society
Secretary, Dr. Patrick J. Grinsell, 1207 Fairchild Ct., Woodland, Calif. 95695. Meets on the fourth Monday, Sept. through May at the Mansion Inn, Sacramento, Calif.

Northwestern New York Radiological Society
Secretary, Dr. Barbara E. Chick, Glens Falls Hospital, Glens Falls, N. Y. 12801.

Northwestern Ohio Radiological Society
Secretary, Dr. Richard W. Siders, 421 Michigan, Toledo, Ohio 43624. Meets 3rd Wednesday from September to May.

Ohio State Radiological Society, Chapter of ACR
Secretary, Dr. James Farmer, Cleveland, Ohio.

Oklahoma State Radiological Society, Chapter of ACR
Secretary, Dr. George H. Ladd, 4616 Denison, Muskogee, Okla. 74401. Meets in January, May and October.

Orange County Radiological Society
Secretary, Dr. William E. Danko, 2601 E. Chapman, Orange, Calif. 92667. Meets on fourth Tuesday of the month, excluding June, July, August, and December, at Orange County Medical Association Bldg., Orange, Calif.

Oregon State Radiological Society, Chapter of ACR
Secretary-Treasurer, Dr. Ray F. Friedman, 3324 S. W. 44th St., Portland, Ore. 97221. Meets on second Wednesday of month, October through April, at the University Club, Portland, Ore.

Orleans Parish Radiological Society
Secretary, Dr. Joseph V. Schlosser, Charity Hospital, New Orleans, La. 70113. Meets second Tuesday of each month.

Pacific Northwest Radiological Society
Secretary-Treasurer, Dr. Kenneth D. Moores, 1118 9th Ave., Seattle, Wash. 98101. Annual Meeting: Benson Hotel, Portland, Ore., May 7–9, 1976.

Pennsylvania Radiological Society, Chapter of ACR
Secretary, Dr. Joseph A. Marasco, Jr., St. Francis General Hosp., Pittsburgh, Pa. 19141.

Philadelphia Roentgen Ray Society
Secretary, Dr. Marvin E. Haskin, 230 N. Broad St., Philadelphia, Pa. 19102. Meets first Thursday of each month at 5 p.m., from October to May in Thompson Hall, College of Physicians.

Pittsburgh Roentgen Society
Secretary, Dr. Klaus M. Bron, Presbyterian-Univ. Hosp., Pittsburgh 15213. Meets second Wednesday of month, September through May, at the Pittsburgh Athletic Association.

Radiation Research Society
Executive Secretary, Richard J. Burk, Jr., 4211 39th St., N.W., Washington, D. C. 20016. Annual Meeting.

Radiological Society of Connecticut, Inc., Chapter of ACR
Secretary, Dr. Gerald L. Baker, 85 Jefferson St., Hartford, Conn. 06106. Meets in Oct., Jan., March, and June.

Radiological Society of Greater Cincinnati
Secretary-Treasurer, Dr. Alvin Nathan, c/o Academy of Medicine, 320 Broadway, Cincinnati, Ohio 45202. Meets first Monday of each month at Cincinnati Academy of Medicine.

Radiological Society of New Jersey, Chapter of ACR
Secretary, Dr. Fred M. Palace, 11 Dale Dr., Morristown, N.J. 07960. Monthly meetings in East Orange and Trenton, N.J. Semi-Annual Meeting in Nov.

Radiological Society of Rhode Island, Chapter of ACR
Secretary-Treasurer, Dr. Daniel J. Alves, Rhode Island Hosp., Providence, R. I. 02902.

Radiological Society of Southern California
Secretary-Treasurer, Dr. A. Franklin Turner, LAC-USC Medical Center, Room 3418, 1200 North State St., Los Angeles, Calif. 90033. Meets three times a year, usually October, February and May.

Radiological Society of the State of New York
Secretary-Treasurer, Dr. John W. Colgan, 273 Hollywood Ave., Rochester, N. Y. 14618.

Redwood Empire Radiological Society
Secretary, Dr. Charles E. Carter, 121 Sotoyome St., Santa Rosa, Calif. 95405. Meets second Monday every other month.

Richmond County Radiological Society
Secretary, Dr. Frederick S. Vines, 11830 Rothbury Dr., Richmond, Va. 23235. Meets third Thursday of each month at the Aberdeen Barn.

Rochester Roentgen Ray Society, Rochester, N. Y.
Secretary-Treasurer, Dr. Robert J. Bruneau, Rochester General Hosp., Rochester, N. Y. 14621. Quarterly meetings on the call of the President, at the Rochester Academy of Medicine.

Rocky Mountain Radiological Society
Secretary-Treasurer, Dr. Lorenz R. Wurtzebach, 4200 E. Ninth Ave., Denver, Colo. 80220. Annual Meeting: Brown Palace Hotel, Denver, Colo., Aug. 19–21, 1976.

San Antonio-Civilian Military Radiological Society
Secretary, Dr. James R. Stewart, Oak Hills Medical Ctr., San Antonio, Tex. 78209. Meets third Wednesday of each month at Fort Sam Houston Officers Club at 6:30 p.m.

San Diego Radiological Society
President, Dr. Donald J. Fleischli, 7849 Fay Ave., La Jolla, Calif. 92037. Meets the first Wednesday of each month Sept. through June at the University Club.

San Francisco Radiological Society
Secretary-Treasurer, Dr. Robert L. Koch, 3838 California St., Suite 106, San Francisco, Calif. 94118.

Section on Radiology, California Medical Association
Secretary, Dr. William H. Graham, 630 East Santa Clara St., San Jose, Calif.

Section on Radiology, Medical Society of the District of Columbia
Secretary-Treasurer, Dr. Albert M. Zelna, 21 Masters St., Potomac, Md. 20854. Meets at Medical Society Library, third Wednesday of January, March, May and October at 8:00 p.m.

Section of Radiology, National Medical Association
Secretary, Dr. Ruby Brooks, Dept. Radiol., Veterans Adm. Hosp., P.O. Box 511, Tuskogee, Ala. 36083. Annual Meeting.

Section on Radiology, Southern Medical Association
Secretary, Dr. Mario A. Calonje, 1514 Jefferson Highway, New Orleans, La. 70121. Annual Meeting.

Section on Radiology, Texas Medical Association
Secretary, Dr. George F. Crawford, St. Elizabeth Hospital, Beaumont, Tex. Meets annually with the Texas Medical Association.

Shreveport Radiological Club
Secretary, Dr. W. R. Harwell, 608 Travis St., Shreveport, La. Meets monthly on third Wednesday at 7:30 p.m., September to May inclusive.

Society for Pediatric Radiology
Secretary-Treasurer, Dr. John P. Dorst, 601 N. Broadway, Baltimore, Md. 21205. Annual meeting: Marriott Hotel, Atlanta, Ga., Sept. 28–29, 1975.

Society of Gastro-intestinal Radiologists
Secretary-Treasurer, Dr. John R. Amberg, University Hospital, 225 W. Dickinson St., San Diego, Calif. 92103.

Society of Nuclear Medicine
Secretary, Dr. E. James Potchen, Edward Mallinckrodt Institute of Radiology, 660 S. Euclid Ave., St. Louis, Mo. 63110. *Administrative Officer*, Mrs. Margaret Glos, 211 E. 43rd St., New York, N. Y. 10017. Annual Meeting.

South Bay Radiological Society
Secretary, Dr. Robert Mindalzun, Valley Radiologists, Inc., 100 O'Connor Dr., San Jose, Calif. 95128. Meets the 2nd Monday of each month at the Santa Clara County Medical Society Bldg., 700 Empey Way, San Jose, Calif.

South Carolina Radiological Society, Chapter of ACR
Secretary, Dr. George W. Brunson, 1406 Gregg St Columbia, S. C. Annual meeting (primarily business) in conjunction with the South Carolina Medical Association meeting in May. Annual fall scientific meeting at time and place designated by the president.

South Coast Radiological Society Chapter of ACR
Secretary-Treasurer, Dr. Richard T. Love, Santa Barbara Med. Clin., 215 Pesetas Lane, Santa Barbara, Calif. 93110. Meets fourth Tuesday of alternate months, Sept., Nov., Jan., March and May.

South Dakota Radiological Society, Chapter of ACR
Secretary, Dr. M. F. Petereit, 2416 S. Phillips, Sioux Falls, S. D. 57105. Meets in spring with State Medical Society and in fall.

Southern California Radiation Therapy Association
Secretary-Treasurer, Dr. Duane J. Gillum, 250 W. Pueblo St., Santa Barbara, Calif. 93105. Meets quarterly.

Southern Radiological Conference
Secretary-Treasurer, Dr. J. W. Maxwell, P.O. Box 2144 Mobile Ala. 36601. Annual Meeting: Grand Hotel, Point Clear, Ala., Jan. 30–Feb. 1, 1976.

Tennessee Radiological Society, Chapter of ACR
Secretary-Treasurer, Dr. Jerry W. Grise, Methodist Hosp., 1265 Union Ave., Memphis, Tenn. 38104. Meets annually at the time and place of the Tennessee State Medical Association meeting.

Texas State Radiological Society, Chapter of ACR
Secretary, Dr. Francis E. O'Neill, 1128 Nix Prof. Bdg., San Antonio, Tex. 78205.

The Fleischner Society
Secretary, Dr. E. Robert Heitzman, State University of New York Upstate Medical Center, Syracuse, N. Y. 13210. Annual Meeting:

Tri-State Radiological Society
Secretary, Dr. Thomas Harmon, St. Mary's Hosp., Evansville, Ind. 47750. Meets bimonthly on the third Wednesday at area Hospitals.

Upper Peninsula Radiological Society
Secretary, Dr. A. Gonty, Menominee, Mich. Meets quarterly.

Utah State Radiological Society, Chapter of ACR
Secretary-Treasurer, Dr. Patrick D. Lester, Dept. Radiol., University of Utah Medical Center, Salt Lake City, Utah 84112. Meets quarterly at Holy Cross Hospital.

Vermont Radiological Society, Chapter of ACR
Secretary, Dr. J. Lorimer Holm, R.R. #3, Barre, Vt. 05641.

Virginia Chapter of ACR
Secretary-Treasurer, Dr. Charles P. Winkler, 3500 Kensington Ave., Suite 2-A, Richmond, Va. 23221.

Washington, D. C., Chapter of ACR
Secretary-Treasurer, Dr. Robert M. Allen, 9312 Convento Terr., Fairfax, Va. 22030.

Washington State Radiological Society, Chapter of ACR
Secretary-Treasurer, Dr. Donald J. Hesch, 3216 N.E. 45th Place, Seattle, Wash. 98105.

West Virginia Radiological Society, Chapter of ACR
Secretary-Treasurer, Dr. Andrew W. Goodwin, II, 200 Med. Arts Bldg., Charleston, W. Va. 25301. Meets concurrently with annual meeting of West Virginia State Medical Society, other meetings arranged by program committee.

Westchester County Radiological Society
Secretary, Dr. Leonard Cutler, 16 Guion Place, New Rochelle, N. Y. 10802. Meets on second Tuesday of October, December, February and May.

Wisconsin Radiological Society, Chapter of ACR
Secretary-Treasurer, Dr. June Unger, Wood VA Hosp., Wood, Wis. 53193. Meets twice a year, May and September.

Wisconsin Society of Therapeutic Radiologists
Secretary, Dr. Alvin Greenberg, Radiother. Ctr., Univ. Hospitals, Madison, Wis. 53706. Meets quarterly.

Wyoming Radiological Society, Chapter of ACR
Secretary, Dr. Ross J. Collie, Box 96, Lander, Wyo. 82520. Meets in fall with State Medical Society and in spring on call of President.

Mexico, Puerto Rico and Central America

Asociación Costarricense de Radiología
Secretary, Dr. Rafael Umaña-Umaña, Apartado 8-5340, San José, Costa Rica.

Asociacón de Radiólogos de Centro America y Panamá. Comprising: Guatemala, El Salvador, Honduras, Nicaragua, Costa Rica and Panamá
Secretary-General, Dr. Francisco Miranbell Solis, Apartado 3352, San José, Costa Rica, Central America. Meets annually in a rotating manner in the six countries.

Sociedad de Radiología de Salvador
Secretary, Dr. Carlos Meijia, 5a Av. Nte. No. 434, San Salvador, Rep. El Salvador.

Sociedad de Radiología de Guatemala
Secretary, Dr. Carlos E. Escobar, 9^2, Calle A 0–05, Zona 1, Guatemala

Sociedad Mexicana de Radiología, A.C.
Coahuila No. 35, México 7, D.F., México.
Secretary-General, Dr. Jorge Cano Coquí. Meets first Monday of each month.

Sociedad Radiológica Panameña
Secretary, Dr. L. Arrieta Sánchez, Apartado No. 6323, Panamá, R. de P. Meets monthly in a department of radiology of a local hospital chosen at preceding meeting.

Sociedad Radiológica de Puerto Rico
Secretary, Dr. César Rosa, Box 9387, Santurce, Puerto Rico 00908. Meets second Thursday of each month at 8:00 P.M. at the Puerto Rico Medical Association Bldg. in San Juan.

British Commonwealth of Nations

Association of Radiologists of the Province of Quebec
121 Boul. Taschereau, Greenfield Park, P. Q., Canada. Meets four times a year.

British Institute of Radiology
Honorary Secretaries, D. H. Traspnell, M. Cohen, 32 Welbeck St., London, W1M/7PG, England.

Canadian Association of Physicists, Division of Medical and Biological Physics
Honorary Secretary-Treasurer, Dr. R. G. Baker, Ontario Cancer Foundation, Ottawa Civic Clinic, 1053 Carling Ave., Ottawa 3, Ont., Canada.

Canadian Association of Radiologists
Honorary Secretary, Dr. Ross O. Hill, Suite 806, 1440 St. Catherine St. West, Montreal 107, Que., Canada. Annual Meeting:

Edmonton and District Radiological Society
Secretary, Dr. L. A. Koller, Suite 360, Professional Bldg., 10830 Jasper Ave., Edmonton 15, Alberta, Canada. Meets third Thursday of each month October to May, except December at various Edmonton Hospitals.

Faculty of Radiologists
Honorary Secretary, P. D. Thomson, 28 Portland Pl., London, W1N 4DE.

Montreal Radiological Study Club
Secretary, Dr. W. Paul Butt, Montreal General Hospital, Montreal, Que., Canada. Meets first Tuesday evening, October to April.

Section of Radiology of the Royal Society of Medicine (Confined to Medical Members)
Meets third Friday each month at 8:15 P.M. at the Royal Society of Medicine, 1 Wimpole St., London, W. 1 M8AE, 1 England.

Société Canadienne-Française de Radiologie
Secretary-General, Dr. Hubert Sasseville, Verdun Hospital, Montréal, P. Q., Canada. Meets every third Tuesday from October to April.

The Hospital Physicists' Association
Honorary Secretary, J. B. Massey, B.Sc., Christie Hosp. and Holt Radium Institute, Physics Department, Withington, Manchester M20 9BX, England.

Toronto Radiological Society
Secretary, Dr. George Wortzman, Toronto General Hosp., Toronto 12, Ont., Canada. Meets second Monday of each month, September through May.

The Royal Australasian College of Radiologists
Honorary Secretary, Dr. T. P. Loneragan, 45 Macquarie St., Sydney, N.S.W. 2000, Australia.

South America

Colégio Brasileiro de Radiologia
Secretary-General, Dr. José Marcos Pires de Oliveira, Caixa Postal 5984, São Paulo, Brazil.

Federación Argentina de Sociedades de Radiología
Branches of the Federation are: Sociedad de Radiólogos de la Provincia de Córdoba; Sociedad Argentina de Radiología; Asociación Argentina de Radiología; Sociedad de Radiología, Radioterapéutica y Medicina Nuclear de Rosario; Sociedad de Radiología y Medicina Nuclear del Centro y Sudeste de la Provincia de Buenos Aires (Mar del Plata); Sociedad Salteña de Radiología y Medicina Nuclear; Sociedad de Radiología de Tucumán; Sociedad de Radiologia del Nordeste Argentino; Sociedad de Radiología de La Plata; and Sociedad de Radiología de San Juan.
Secretary-General-Treasurer, Dr. Roberto Habichayn, Av. Colón 637, Córdoba, Argentina.
Congress will be organized by Sociedad de Radiología, Radioterapéutica y Medicina Nuclear de Rosario in 1975.

Sociedad Argentina de Radiología
Secretary-General, Dr. Alba de la Torre, Santa Fé 1171, Buenos Aires, Argentina. Meets first Wednesday evening, April through December.

Sociedad Boliviana de Radiología
Secretary, Dr. Javier Prada Méndez, Casilla 1182, La Paz, Bolivia. Meets monthly. General assembly once every two years.

Sociedade Brasileira de Radiologia
Secretary, Dr. Armando Rocha Amoédo, Caixa Postal 1532, Rio de Janeiro, Brazil. General Assembly meets every two years in December.

Sociedade Brasileira de Radioterapia
Luiz Antonio, 644, São Paulo, Brazil. Meets monthly on second Wednesday at 9:00 P.M. in São Paulo at Av. Brigadeiro Luiz Antonio, 644.

Sociedad Chilena de Radiología
Secretary, Dr. Manuel Neira, Casilla 13426, Santiago, Chile. Meets first Friday of each month at Av. Santa María 1810 at 7:00 P.M.

Sociedad Colombiana de Radiología
Secretary-General, Dr. Gustavo Sánchez Sánchez, Bogotá, Colombia. Meets last Thursday of each month.

Sociedad Ecuatoriana de Radiología
Secretary, Dr. Luis Blum, Casilla 3712, Guayaquil, Ecuador.

Sociedad Paraguaya de Radiología
Secretary, Dr. Hugo Volpe Rios, 15 de Agosto 322, Asunción, Paraguay.

Sociedad Peruana de Radiología
Secretary-General, Dra. Ladis Delpino, Av. General Santa Cruz No. 315, Miraflores, Lima, Perú, Casilla Correo, 2306, Lima, Perú. Meets monthly except during January, February, and March.

Sociedad de Radiología del Atlantico
Secretary, Dr. Raul Fernandez, Calle 40 #41-110, Barranquilla, Colombia. Society meets monthly at the Instituto de Radiología.

Sociedad de Radiología del Nordeste Argentino
Secretary-General, Dr. Francisco J. Velar, Catamarca 561, Corrientes, Argentina.

Sociedad de Radiología de La Plata
Secretary, Dr. Hiram D. Haurigot, Calle 50 No. 374, La Plata, Argentina.

Sociedad de Radiología, Cancerología y Física Médica del Uruguay
Secretary-General, Dr. Manuel Gonzáles Maseda, Av. Agraciada 1464, piso 13, Montevideo, Uruguay.

Sociedade de Radiología de Pernambuco
Secretary, Dr. Manoel Medeiros Instituto de Radiologia da Faculdade de Medicina da Universidade do Recife, Caixa Postal 505, Pernambuco, Brazil.

Sociedad de Roentgenología y Medicina Nuclear de la Provincia de Córdoba
Secretary-General, Dr. Lucas C. Di Rienzo, Ave. Grl. Paz. 151, Córdoba, Argentina.

Sociedad de Radiología, Radioterapéutica y Medicina Nuclear de Rosario
Secretary-General, Dr. Federico Frágola, Santa Fe 1798, Rosario, Argentina.

Sociedad Salteña de Radiología y Medicina Nuclear
Treasurer, Dr. Julio Luis Baldi, Av. Sarmiento 536, Salta, Argentina.

Sociedad Venezolana de Radiología y Medicina Nuclear
Secretary-General, Dr. Salvador Itriago Borgas, Apartado Postal 9213, Candelaria, Caracas, Venezuela. Meets monthly, third Friday at Colegio Médico del Distrito Federal, Caracas.

Continental Europe

Österreichische Röntgen-Gesellschaft
Secretary, Dr. Ernst Kotcher, Wiener Allgemeine Poliklinik Mariannengasse 10, A-1090 Wien, Austria. Meets second Tuesday of each month in Allgemeine Poliklinik.

Société Royale Belge de Radiologie
General Secretary, Dr. Joseph Baeyens, Alost, Belgium. Meets in February, March, May, June, September, October, November and December.

Société Européenne de Radiologie Pédiatrique
Secretary, Dr. J. Corbaton, Clinica Infantil "La Paz," Av. Generalissimo, 117 Madrid 34, Spain. Annual Meeting:
Permanent Secretary, Clément Fauré, Hôpital des Enfants Malades, 149, rue de Sèvres, 75 730, Paris Cadet 15, France.

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ABSTRACTS OF RADIOLOGIC LITERATURE

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ROENTGEN DIAGNOSIS

HEAD

LLOYD, G. A. S., BARTRAM, C. I., and STANLEY, P. Ethmoid mucocoeles. *Brit. J. Radiol.*, Oct., 1974, *47*, 646–651. (From: The Royal National Nose, Throat and Ear Hospital, and Moorfields Eye Hospital, London, England.)

A mucocele of one of the paranasal sinuses consists of a dilated mucus-containing sac lined with epithelium of the sinus, and it occurs because of continuing fluid secretion into an obstructed cell. It may result from infection, trauma, pressure from a mass, or cystic degeneration of the mucosa. It occurs commonly in the frontal sinus and is usually not a diagnostic problem, but when it occurs in the ethmoid cells, the early changes may be subtle.

Clinically the patients usually present with a mass in the medial canthus, proptosis, epiphora, or a combination of these. Twelve patients with ethmoid mucoceles are reported here and all presented with a mass at the medial canthus. Some had epiphora and some had lateral displacement of the globe and diplopia. The ages of these patients varied between three and 64 years. The smallest mucocele in the series was recognized initially at dacryocystography, done in investigation of epiphora. In the small mucoceles, which presented nevertheless as masses, the earliest roentgen feature was loss of translucence in the ethmoid cells, and this is a non-specific observation. Another characteristic was loss of the vertical line forming the anterior component of the medial wall of the orbit: six showed an expanded bony orbita rim. Destruction of the ethmoid septa was observed in four, and expansion of the mucocele into the frontal sinus was observed in two patients.

By far the most accurate and successful method of demonstrating the lesion is tomography, and this method is advocated in any patient with a mass in the medial canthus or the possibility of an ethmoid mucocele. Axial tomography is even more satisfactory than that in the coronal plane and shows both the expansion of the mucocele and the soft tissue mass in the orbit. Axial tomography can spare the patient further examinations such as orbital venography or carotid angiography.—*E. Frederick Lang, M.D.*

NECK AND CHEST

SHERBON, K. J. Traumatic rupture of the thoracic aorta—the radiologist's responsibility. *Australasian Radiol.*, June, 1975, *19*, 164–171. (From: Royal Prince Alfred Hospital, Camperdown, N.S.W., 2050, Australia.)

Traumatic rupture of the thoracic aorta is a very serious injury with few patients handled fast enough to prevent sudden death. A series of 275 cases is recorded in which only two patients survived more than four years.

Eight patients with aortic ruptures are presented and detailed histories of several of these are recorded. In addition one patient with long term follow-up is also described and included in the series.

Plain chest film findings include widening of the mediastinum, obliteration of the aortic knuckle, and displacement of the trachea toward the right. These are the findings which must lead the radiologist to suspect the nature of these lesions.

Aortographic findings are described and illustrated. False aneurysms located just distal to the left subclavian origin and most often on the inner aspect of the aortic curve were seen in eight out of the total of nine patients. Flaps of torn aortic wall could be seen as linear defects in the contrast medium.

This article is well illustrated with numerous excellent reproductions of chest x-rays and aortograms. It will undoubtedly accentuate the growing awareness of the frequency of traumatic rupture of the aorta following closed chest injury. Plain chest x-rays should alert the radiologist to the possibility and aortography performed from the femoral artery or from an axillary approach is necessary to give unequivocal evidence of the rupture and show the precise anatomic area of injury.—*Richard E. Kinzer, M.D.*

THURAIRAJASINGHAM, S., DHARMASENA, B. D., and KASTHURIRATNA, T. Pulmonary alveolar microlithiasis. *Australasian Radiol.*, June, 1975, *19*, 175–180. (From: Government General Hospital, Kandy, Sri Lanka.)

Two cases of pulmonary alveolar microlithiasis, with the diagnosis established on clinical and radiological grounds only, are reported and added to less than 100 previously reported cases in the world literature. It is unfortunate that lung biopsy could not have been a part of the diagnosis in these two patients.

Felson has described a roentgen sign which he believes is diagnostic of this condition. "The pleura appears as a negative shadow, *i.e.*, a black line instead of a white one, because it lies between the bony rib cage and the calcified pulmonary infiltrate." He further notes that on an over-exposed Bucky film, even the heart shadow appears black by contrast. This sign has also been noted in a case of hyperparathyroidism with extensive pulmonary calcinosis. —*Richard E. Kinzer, M.D.*

NO AUTHOR. Factors influencing survival after resection for bronchogenic carcinoma: analysis of 1,118 cases. *Chinese M. J.*, Sept., 1975, *1*, 361–368. (From: Shanghai Chest Hospital, Shanghai, China.)

Over 1,000 patients with bronchogenic carcinoma who were operated on at the Shanghai Chest Hospital between 1957–1972 are included in this study; 107 survived 5–14 years after surgery. Factors contributing to survival include: age; occupation; time lapse between symptoms and operation; size, location, histology of tumor; absence of cavitation or central necrosis. The authors consider their five year survival rate of 27.2 percent in need of improvement. This will be achieved by "new successes . . . in the prevention and treatment of bronchogenic carcinoma under the guidance of Chairman Mao's revolutionary line." Furthermore, they intend to assiduously "follow the road of integrating ourselves with the workers, peasants and soldiers, and to remould our world outlook. In medical work we are determined to sum up our experience seriously so as to further improve the results of treatment, to take an active part in the prevention and treatment of bronchogenic carcinoma, and to serve the patients wholeheartedly."—*Lois Cowan Collins, M.D.*

Kretzschmar, R. Über atelektatische Pseudotumoren der Lunge (Rundatelektasen). (Atelectatic pseudo-tumors of the lung: round atelectases.) *Fortschr. a. d. Geb. d. Röntgenstrahlen u. d. Nukleramedizin*, Jan., 1975, *122*, 19–29. (Address: Koningin Juliana Ziekenhuis, Röntgenafdeling, Boerhaavelaan 65, Hengelo (Ov.), Netherlands.)

Round atelectases were diagnosed in six of five patients (two radiologically and pathologically, four radiologically only). They are caused by infolding of the pleura, usually in the vicinity of the lower lobe edges, and occur during the healing phase of exudative pleuritis or pneumothorax. The radiological features of round atelectasis are round peripheral densities of varying size which are associated with the well-known indirect signs of atelectasis. These round densities are typically located posteriorly in the region of the basal lobar edges and might be visible only in the lateral projection. Bronchography reveals multiple subsegmental cut-offs and crowding of bronchi with evidence of loss of volume and compensatory hyperaeration of neighboring lung regions. These findings can also be demonstrated with tomography which, in addition, visualized the associated pleural changes. This results in a typical tomographic appearance. Since round atelectases can get quite large, the term "atelectatic pseudo-tumor of the lungs" is suggested.—*Peter F. Winter, M.D.*

ABDOMEN

Tabár, L., Somogyi, J., and Böhm, K. Pneumoperikardium traumatischen Ursprungs. (Pneumopericardium of traumatic origin.) *Fortschr. a. d. Geb. d. Röntgenstrahlen u. d. Nuklearmedizin*, Dec., 1974, *121*, 698–701. (Address: Dr. L. Tabár, Radiologische Klinik der Medizinschen Universität, 7643 Pécs/Ungarn, Hungary.)

Pneumopericardium is considered an uncommon condition and can usually be attributed to an underlying trauma. Two pertinent cases are reported.

The first patient, a 24 year old man, while returning from a drinking spree late at night suddenly felt a dull pain in the liver region as if he had been hit. On hospital admission the entrance wound of a bullet was noted in the right subcostal region anteriorly. There was no exit wound. Roentgen examination disclosed minimal free air under the right hemidiaphragm and a marginal pneumopericardium on the right side upward toward the aorta. On the lateral view a bullet could be identified slightly posterior to the barium-filled esophagus. Three days later the pneumopericardium could no longer be seen.

The second patient, a 53 year old man, had jumped from the third floor of a house in a suicide attempt. He suffered multiple fractures of porotic bones, especially the ribs. Roentgenologically, there was a marginal pneumothorax in the left upper chest together with a pleural effusion. Of special interest was a right-sided pneumopericardium which extended alongside the right heart border upward toward the aorta. In this case it is reasoned that a fragment of a fractured rib had perforated the pericardium.

Although trauma represents a frequent cause of an obscure pneumopericardium, other causes must also be considered in the differential diagnosis.—*Ernest Kraft, M.D.*

Kido, Choichiro. Primary liver cancer (angiography and scintigraphy.) *Australasian Radiol.*, June, 1975, *19*, 129–139. (From: Department of Diagnostic Radiology, Aichi Cancer Center Hospital, Tashiro-cho, Chikusa-ku, Nagoya, Japan.)

Selective angiography and liver scanning with radioisotopes are significant aids in localizing primary liver carcinoma. Development of a test for a_1-fetoprotein has given us help in the qualitative diagnosis of hepatocellular carcinoma among the primary liver cancers.

These methods have limitations, however, and five cases among a series of 67 of primary hepatic carcinoma, are presented to illustrate the difficulties in diagnosis which have been encountered.

Liver scanning in case I indicated marked compression of the left lobe of the liver from the outside, suggesting extrahepatic tumor. Selective and superselective arteriograms showed a dilated common hepatic artery, and the right hepatic artery was dilated at its origin. The left hepatic artery was also dilated and it presented a picture of proliferating, abnormally dilated vessels in the periphery with tumor stain extending down to the fourth lumbar vertebra. a_1-Fetoprotein was positive and left lobular hepatectomy was accomplished and revealed a well differentiated hepatocellular carcinoma. Case II was a symptom free male with esophageal varices found on a routine health check-up. Liver scan showed marked splenomegaly with typical picture of liver cirrhosis, and a small localized defect in the upper pole of the right lobe. Positive a_1-fetoprotein was demonstrated. The angiograms were positive and the presence of metastatic lesions in the lungs seems to make the diagnosis of hepatocellular carcinoma definite, although this patient is still being studied.

Case III was a male presenting with fever, right abdominal pain and enlargement of the liver. a_1 Fetoprotein was negative, but liver scan and arteriograms were positive and the diagnosis of hepatocellular carcinoma of undifferentiated type was confirmed at laparotomy. Autopsy revealed cholangiocarcinoma throughout the liver in Case V. There was a cord-like structure of hepatocellular carcinoma only at the hilum. a_1-Fetoprotein was positive as was the liver scan, but angiograms failed to show proliferation of abnormal blood vessels, tumor stains, arteriovenous shunts or even luminal irregularities.

The illustrations are of good quality and an interesting analysis of angiographic findings in primary liver cancer is documented along with an attempt to compare angiographic and scanning pictures. In the 51 cases of verified hepatocellular carcinoma, a_1-fetoprotein (A.F.P.) was positive in 75 percent.—*Richard E. Kinzer, M.D.*

HAERTEL, M., and FUCHS, W. A. Angiography in pancreatic trauma. *Brit. J. Radiol.*, Oct., 1974, *47*, 641–645. (From: Department of Diagnostic Radiology, University Hospital, Inselspital, CH-3010 Bern, Switzerland.)

Among 125 patients who were investigated by angiography following blunt abdominal trauma there were four with traumatic lesions of the pancreas, seen in a hospital in Switzerland. Of these four, two had solitary pancreatic injuries and the other two had lacerations of more than one abdominal organ. The injuries usually occur following compressive abdominal force, and because of the resistance of the spine it is usually the pancreatic head which suffers.

The angiographic features of a traumatic lesion of the pancreas are occlusion of pancreatic arteries and local impairment of arterial circulation. A collateral circulation may develop, particularly in the head of the pancreas. Displacement of the pancreatic arteries indicates the presence of an adjacent hematoma. Occasionally a large mass may displace the duodenum, stomach, or proximal jejunum and the arteries supplying these structures. Extravasation of contrast medium was not observed in these four patients and is apparently a rare occurrence.

A hematoma or edema may lead to compression of the splenic vein or obstruction of it, and therefore the venous phase of the celiac and mesenteric angiograms is significant. The splenic and portal vein may be displaced due to a hematoma or edema. Differentiation between hematoma, abscess, and pancreatic pseudocyst cannot be made by angiography, and post-traumatic pancreatitis is indistinguishable from inflammatory disease of other origin. Bleeding into the pancreatic duct from post-traumatic pseudoaneurysms of the splenic artery is another rare complication of pancreatic trauma.

The reliable angiographic findings are vascular laceration, and displacement due to a hematoma or edema.—*E. F. Lang, M.D.*

GENITOURINARY SYSTEM

SCHMIDT, M. Das spontane perirenale Hämatom als Komplikation der chronischen Pyelonephritis. (Spontaneous peri-renal hematoma as a complication of chronic pyelonephritis.) *Fortschr. a. d. Geb. d. Röntgenstrahlen u. d. Nuklearmedizin*, Feb., 1975, *122*, 112–115. (Address. Chefarzt der Radiologischen Abt. des Stadtkrankenhauses, 86 Bamberg, Sandstrasse, Germany.)

Three cases of spontaneous peri-renal hematoma are described. The spontaneous peri-renal hematoma is a rare complication of chronic pyelonephritis and only a few cases have been reported in the literature. The etiology of the spontaneous hematoma in chronic pyelonephritis is probably related to inflammatory destruction with rupture of vessels. The spontaneous peri-renal hematoma occurs in an acute and chronic form. The acute form presents with a palpable abdominal mass associated with abdominal distention, pain and vomiting. This can be mistaken for a hollow viscus perforation. The intravenous pyelogram reveals an enlarged kidney without excretion; the differential diagnosis of this finding includes hydronephrosis, tumor and perinephric abscess. The follow-up intravenous pyelogram after the acute symptoms have subsided shows normal excretion without evidence of an intrarenal space-occupying process. The chronic form presents with a palpable tumor associated with dull flank pain and/or macrohematuria. The angiogram, which is usually performed in these cases, shows a space-occupying perirenal process. While this finding is not diagnostic, in context with the clinical setting the diagnosis of a spontaneous peri-renal hematoma should be considered. However, surgical confirmation should be obtained in all patients.—*Peter F. Winter, M.D.*

CHANDIE SHAW, M. P. Kalkmilch der Niere: 5 Beobachtungen in hydronephrotischen Nieren. (Milk of calcium in the kidney: observations of five cases with hydronephrosis.) *Fortschr. a. d. Geb. d. Röntgenstrahlen u. d. Nuklearmedizin*, Feb., 1975, *122*, 116–119. (Address: Radiolog, Abt. des St. Elisabeth's of Groote Gasthuis Haarlem, NL-Haarlem, Netherlands.)

Only eleven cases of milk of calcium in hydronephrosis have been reported in the literature. The author has been able to observe five additional cases in a period of 14 months. In three patients, the cause of the hydronephrosis was a stone at the ureteral-pelvic junction, and in the other two cases a ureteral stenosis below the pelvis was present. Although milk of calcium in the kidney may be mistaken for a solid renal calculus, recognition of special features of renal calcification on vertical beam roentgenograms should lead to the proper diagnosis. The roentgenologic features, which have been previously described by Murray, are: (1) atypical location of calcium density within the kidney; (2) often unusually large size of calcification; (3) nearly circular shape of calcification; (4) low calcium density in relation to apparent size; and (5) fuzzy indistinct margins of calcification. These criteria are, however, not always reliable and the first criterion was not applicable in any of the patients in this report.—*Peter F. Winter, M.D.*

SKELETAL SYSTEM

KAMHI, EDOUARD, and MACEWEN, G. DEAN. Treatment of Legg-Calvé-Perthes disease: prognostic value of Catterall's classification. *J. Bone & Joint Surg.*, July, 1975, *57*-A, 651–654. (Address: Edouard Kamhi, M.D., 325 Park Avenue, Huntington, N. Y. 11743.)

The authors utilize the classification suggested by Catterall which places patients in four groups in order of increasing severity of involvement of the femoral head. Group I includes involvement of only the anterior part of the epiphysis with no collapse and no sequestrum formation. Group II involves up to 50 percent of the epiphysis and there is sequestrum formation, however, the presence of uninvolved medial and lateral portions of the epiphysis prevents collapse of the head. In Group III, three-quarters of the epiphysis is affected, collapse occurs, and a large sequestrum forms. In Group IV the entire epiphysis is involved and collapse occurs early and may be severe. Apparently there is a direct correlation between the severity of involvement and the prognosis. The authors correlate the degree of femoral head involvement with method of treatment, there being two basic methods of treatment, non-containment methods and containment methods. The latter defined as abduction and internal rotation of the extremity until the femoral epiphysis is well within Perkin's line.

A method of rating results was devised based upon sphericity of the femoral head as measured by means of a transparent template with circles drawn at 2 mm intervals. A deviation less than 2 mm on both anteroposterior and lateral roentgenograms was considered good, one with a deviation from a circle equal to 2 mm, fair, and a deviation of more than 2 mm, poor. Difference in Groups III and IV as treated by non-containment methods and by containment methods showed approximately one-half as many poor results. These differences were more significant the younger the patients. Patients of any age with Group I involvement and in those below six years old with Group II involvement showed no poor results regardless of method of treatment. Involvement of the epiphyseal plate can affect the prognosis because of premature closure of the epiphyseal plate. An open growth plate represents a remodeling potential so that the end result at maturity depends on the remaining remodeling potential and the time that is left for the remodeling process. The characteristic appearance of each Catterall rating does not develop until the disease process is well into the stage of fragmentation.

On the basis of the findings of these authors it appears that once the sequestrum is absorbed and regeneration is under way, further deterioration does not occur if motion is maintained and the femoral head is not grossly subluxed.—*Lionel W. Young, M.D.*

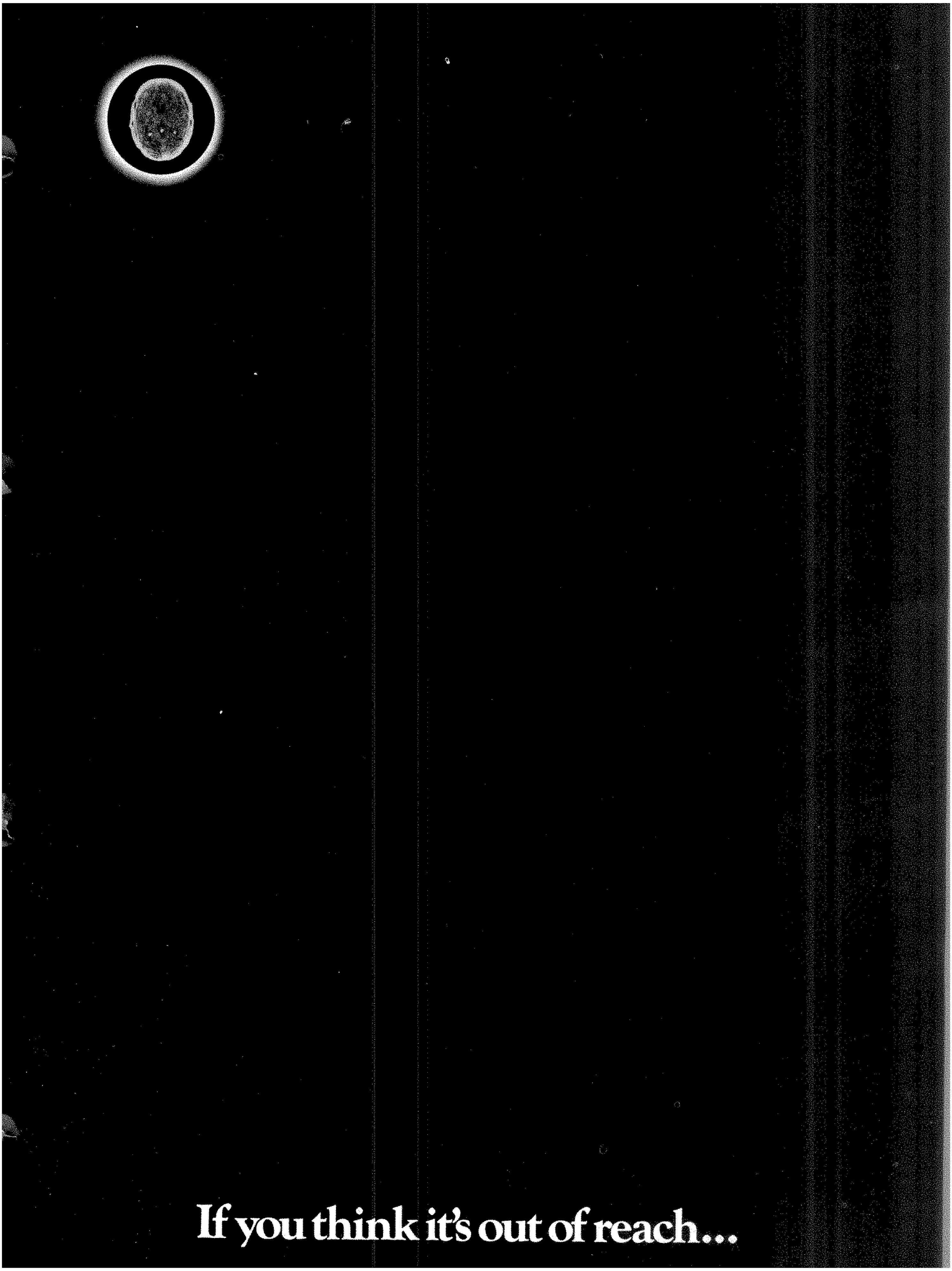
DEPUEY, E. GORDON, THOMPSON, WAYNE L., ALAGARSAMY, VEERASAMY and BURDINE, JOHN A. Bone mineral content determined by functional imaging. *J. Nuclear Med.*, Oct., 1975, *16*, 891–895. (Address: J. A. Burdine, M.D., Nuclear Medicine Section, Department of Radiology, Baylor College of Medicine, Houston, Texas 77025.)

Photon absorptiometry is a simple and accurate method for determining changes in bone volume and mineral content in serial studies.

The os calcis was the site studied due to its relatively large size, little overlying soft tissue and accessibility. The patient's heel was placed in a Plexiglas trough filled with water and then placed between the photon source (40-mCi ^{241}Am which is a 60 keV emittor) and the scintillation camera. Data were obtained and a formula was used to determine the bone mineral index (BMI).

Three cases were presented. Two cases dealt with the thyroid gland and showed changes in the BMI as the thyrotoxic symptoms decreased in one case and increased in the other. Hyperthyroidism causes a decreased BMI. Case 3 had a metastatic carcinoma of the breast with an elevated serum calcium which dropped temporarily after receiving 2 mg of mithramycin. The drop in the serum calcium was reflected by a rise in the BMI.

The value of the BMI determination relates not only to research pertaining to calcium metabolism in various gastrointestinal, vitamin deficiency, endocrine and renal disorders but also to a clinical need for a means of monitoring such changes.—*Charles W. Cooley, M.D.*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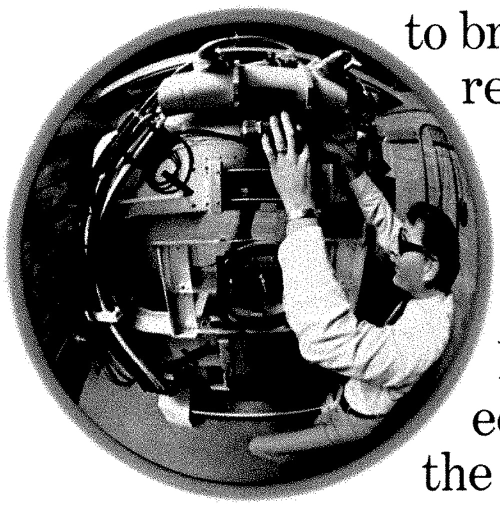

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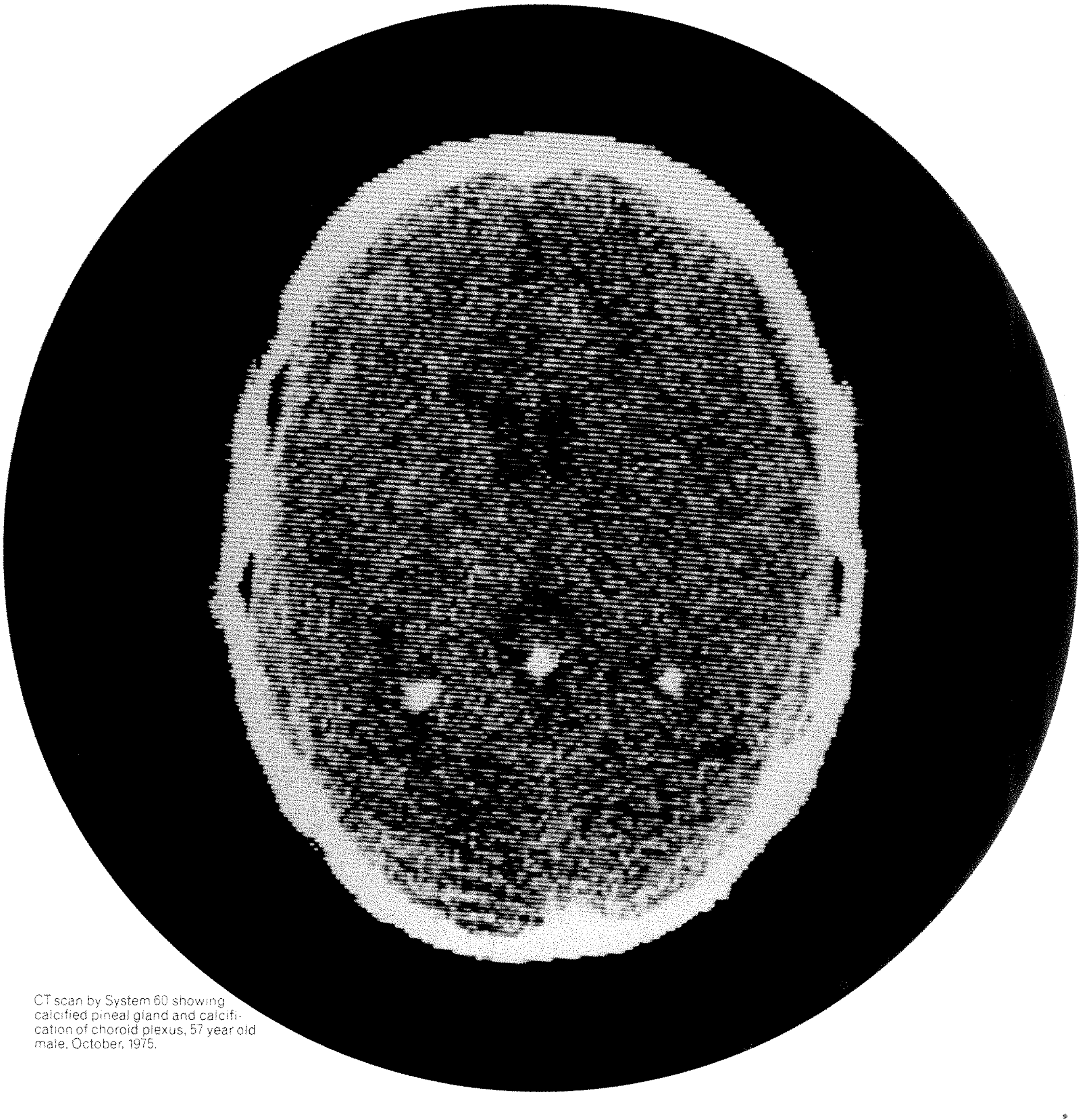

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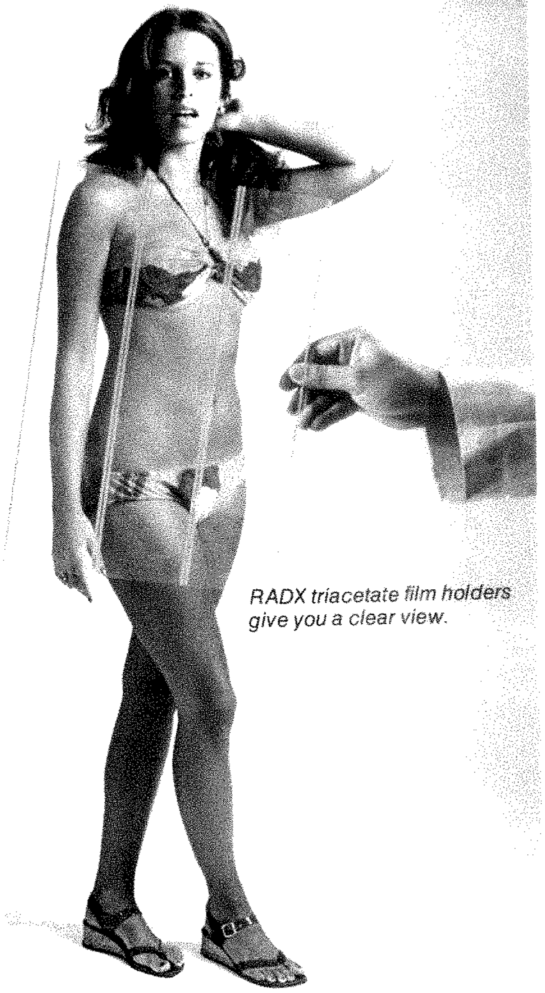

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Improved Diagnostic Clarity at Conventional Speed	Cronex® 7/Quanta II	Low Haze. Low noise. Clarity like Cronex® 2DC but with 90-second processing. Speed equal to Cronex® 4/Hi-Plus.
High Speed with Excellent Visualization of Bone Detail and Soft Tissue	Cronex® 6 Plus/Quanta II	Superb low-density contrast. Extended recording range. Twice the speed of Cronex® 4/Hi-Plus.

can increase system speeds diagnostic clarity.

Excellent Diagnostic Clarity

Quanta II screens provide diagnostic clarity similar to Cronex® Hi-Plus. The increased speed means there is less chance of blurred images caused by patient motion. In addition, since smaller focal spots can be used, Quanta II is ideal for specialized procedures such as magnification angiography.

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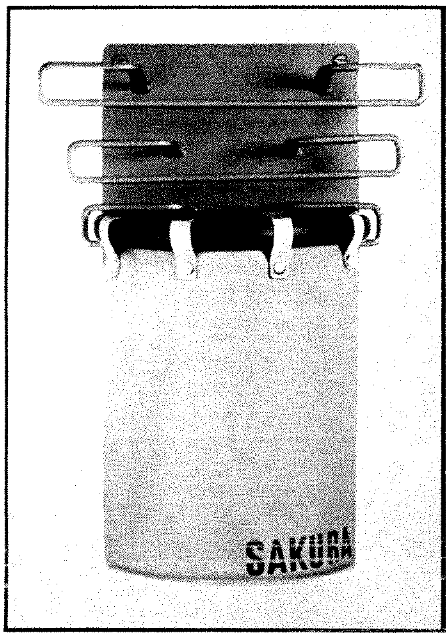

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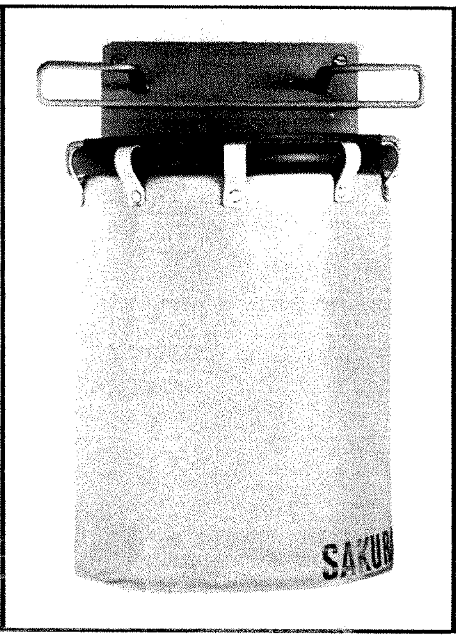

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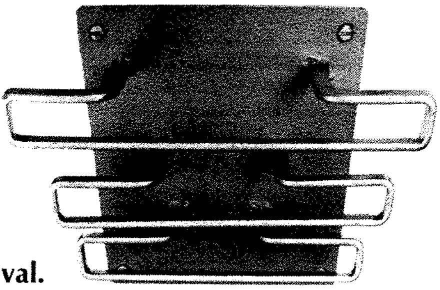

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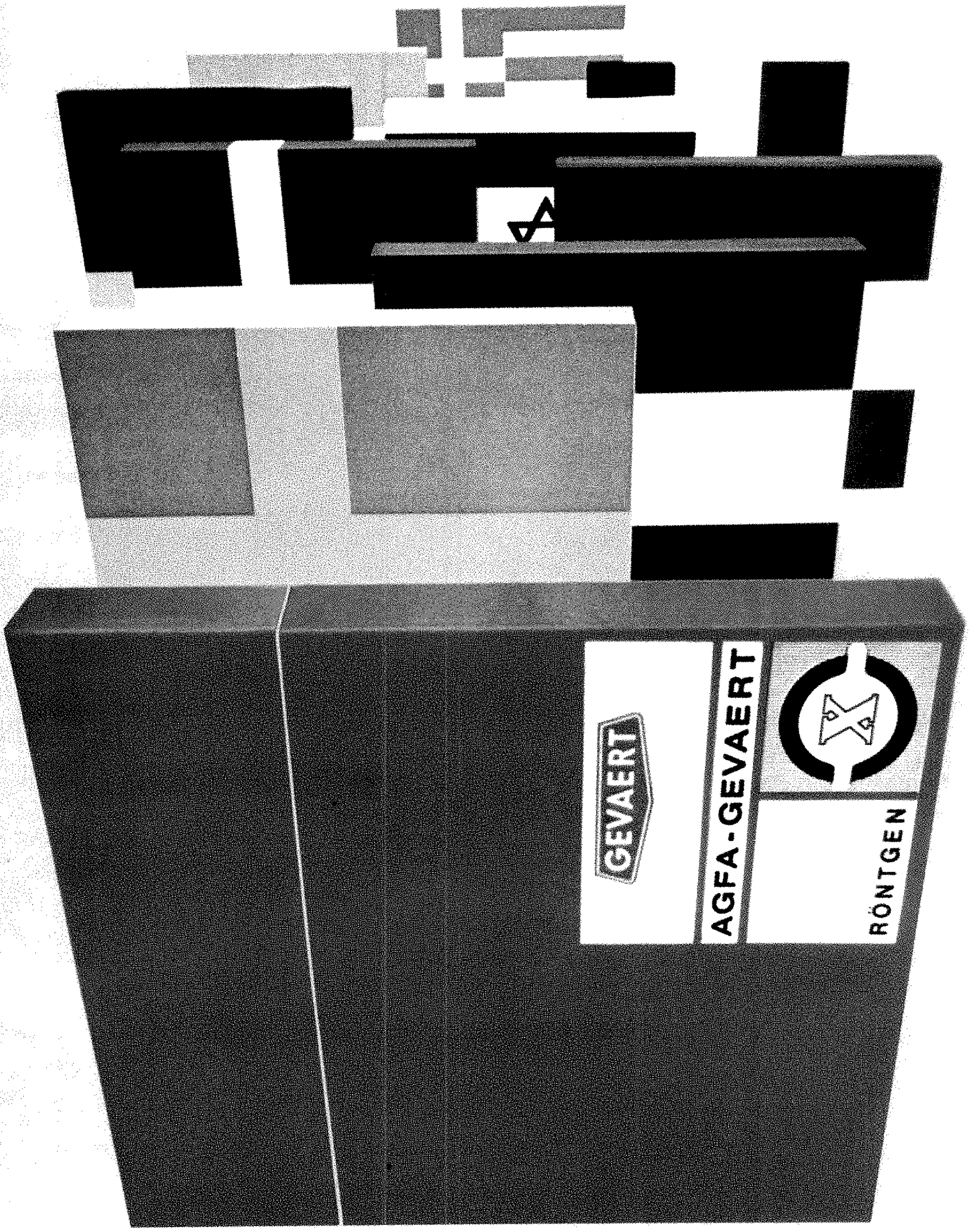

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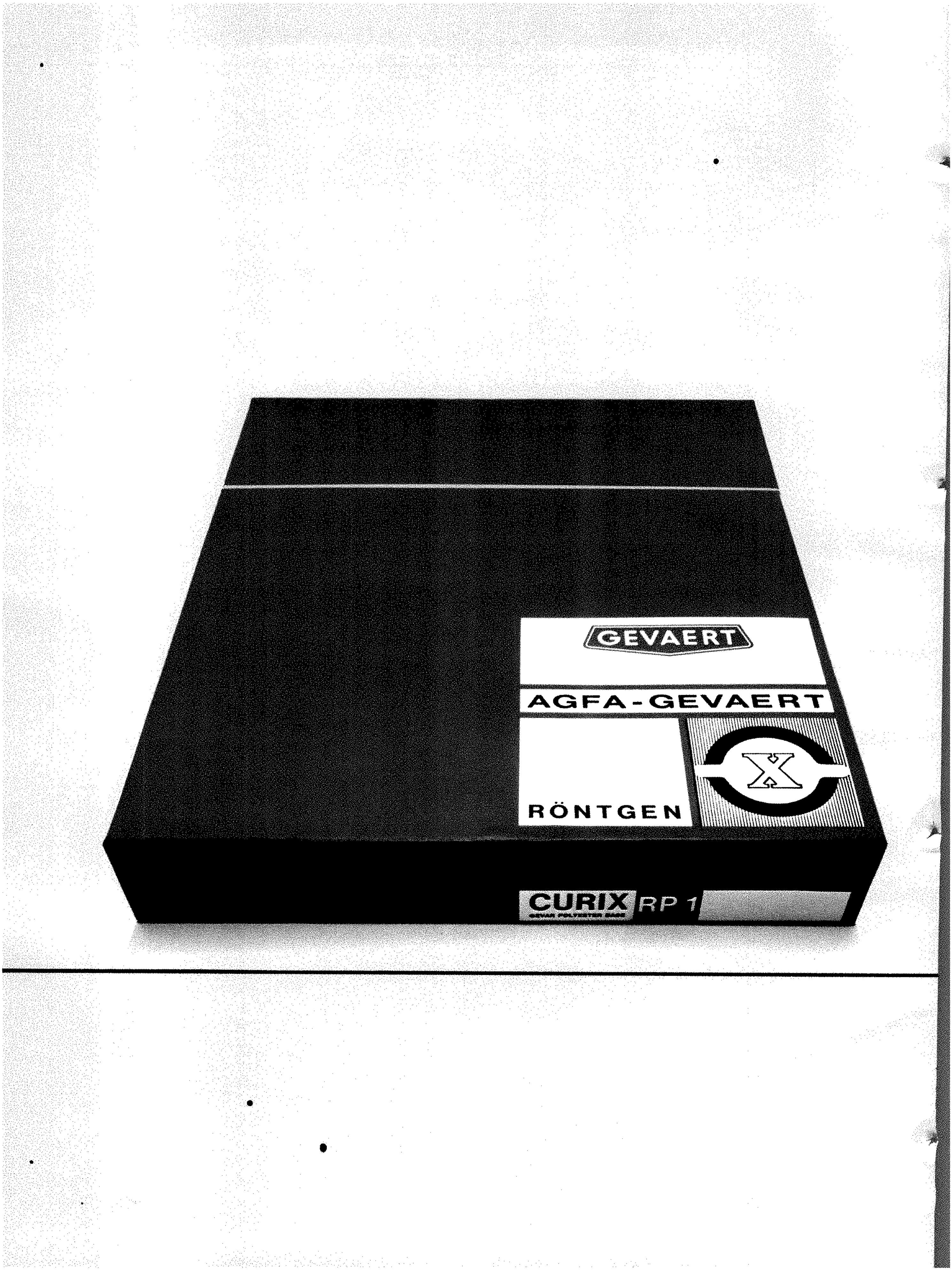

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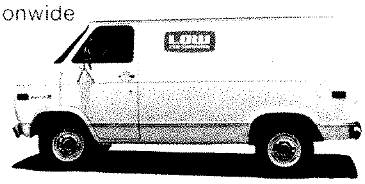

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PRINCIPLES OF RADIOGRAPHIC EXPOSURE AND PROCESSING (2nd Ed., 11th Ptg.) *by* **Arthur W. Fuchs**, *Rochester, New York.* Describes a simple though exact exposure system which is based upon proved fundamental theories and practices. Wherever possible, the exposure factors have been reduced to constants, thereby eliminating many sources of possible error. Discusses in detail the operations necessary to the correct handling and chemical treatment of exposed x-ray film to convert it to a radiograph. Complete details are provided for the development, rinsing, fixing, washing and drying processes. A fourteen page glossary of terms and techniques is provided. *'74, 304 pp. (7 x 10), 600 il., $14.25*

DIAGNOSTIC AND THERAPEUTIC AIDS IN UROLOGY *edited by* **Henry Bodner**, *Loma Linda Univ. School of Medicine, Los Angeles. In Collaboration with* **John S. Arconti, Jr., Allan H. Howard** *and* **Robert O. Pearman.** *(150 Contributors)* This comprehensive survey outlines valuable "tricks of the trade" which do not appear in standard textbooks on urology. It includes innovative uses of standard equipment and instruments, equipment from other specialties, and materials easily obtainable outside the medical field. It has been oriented toward diagnosis, application in office or at bedside, and in the operating room. *'74, 376 pp. (6 3/4 x 9 3/4), 82 il., 5 tables, $24.75*

CARDIAC CATHETERIZATION AND ANGIOCARDIOGRAPHY IN SEVERE NEONATAL HEART DISEASE *by* **Michael T. Gyepes**, *UCLA, Los Angeles, California, and* **William R. Vincent**, *Pennsylvania State Univ., University Park, Pennsylvania.* Written primarily for trainees in pediatric cardiology and pediatric cardiovascular radiology, this book presents a concise and logical approach to the diagnosis of severe congenital heart disease in the newborn. The authors present a broad functional classification of the lesions which most often cause symptoms in the first month of life. The book is extensively illustrated. *'74, 184 pp., 317 il., $14.50*

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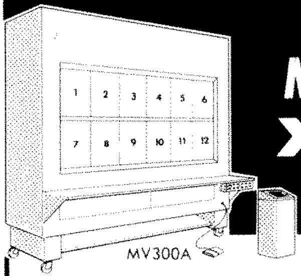

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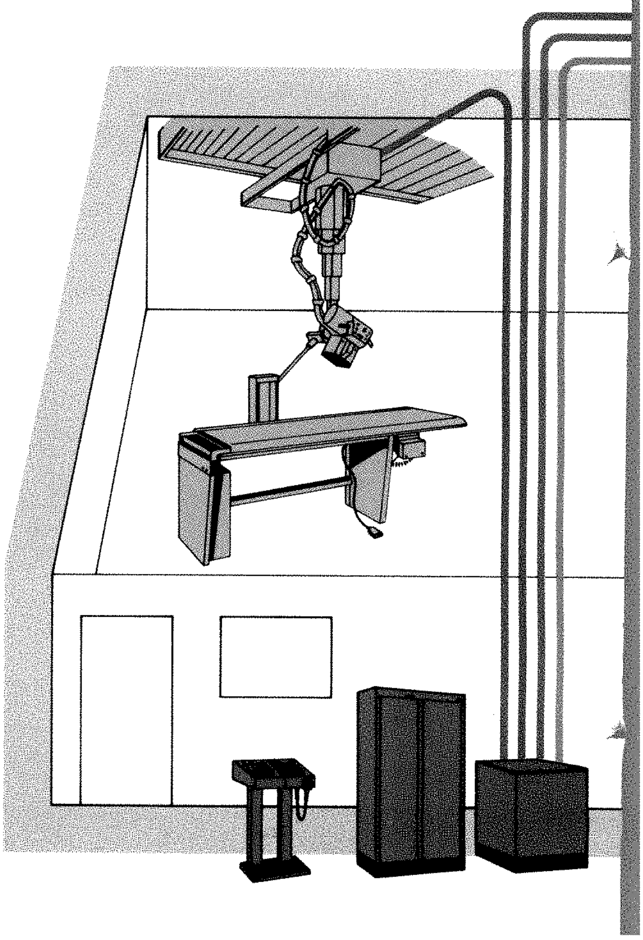

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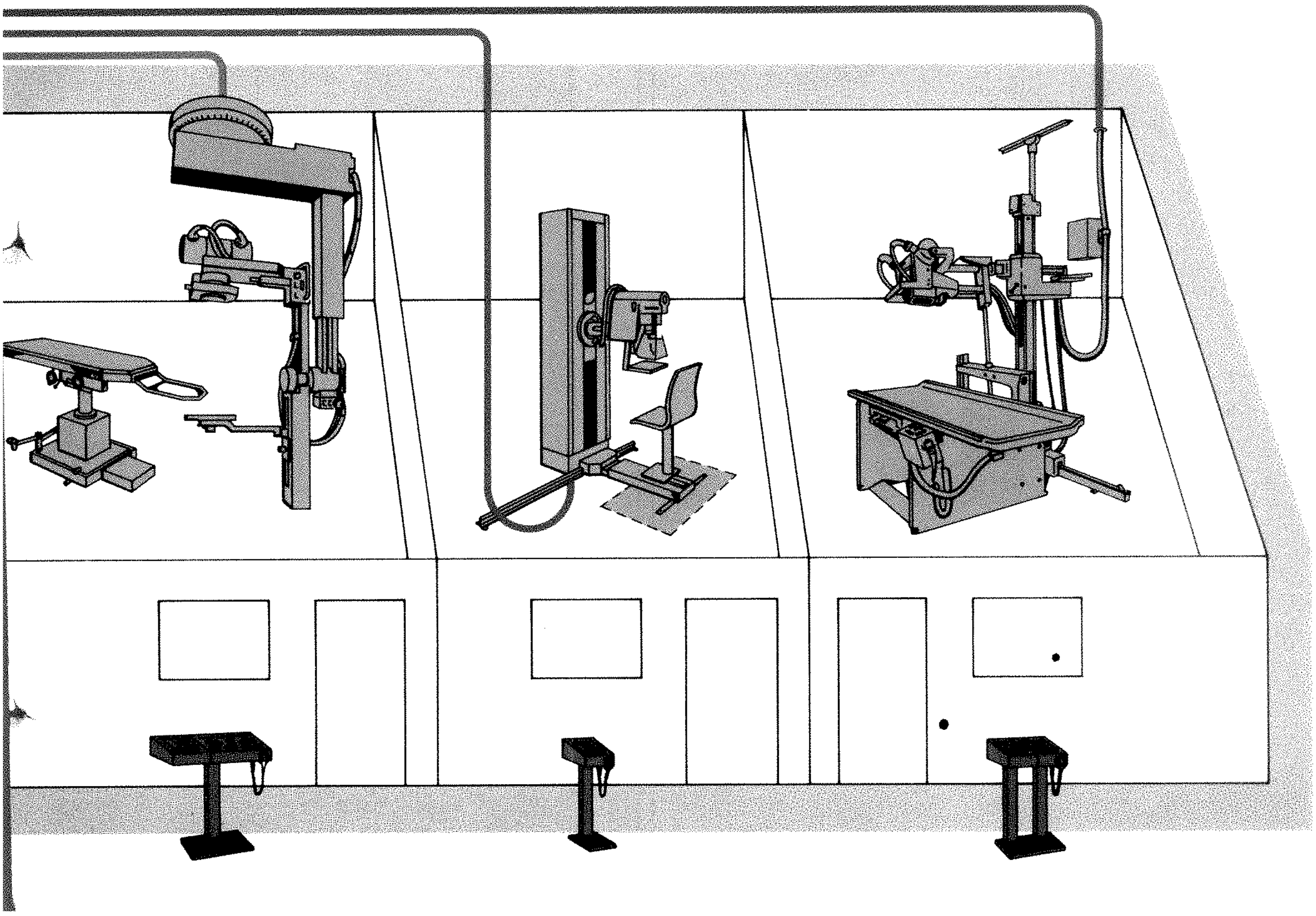

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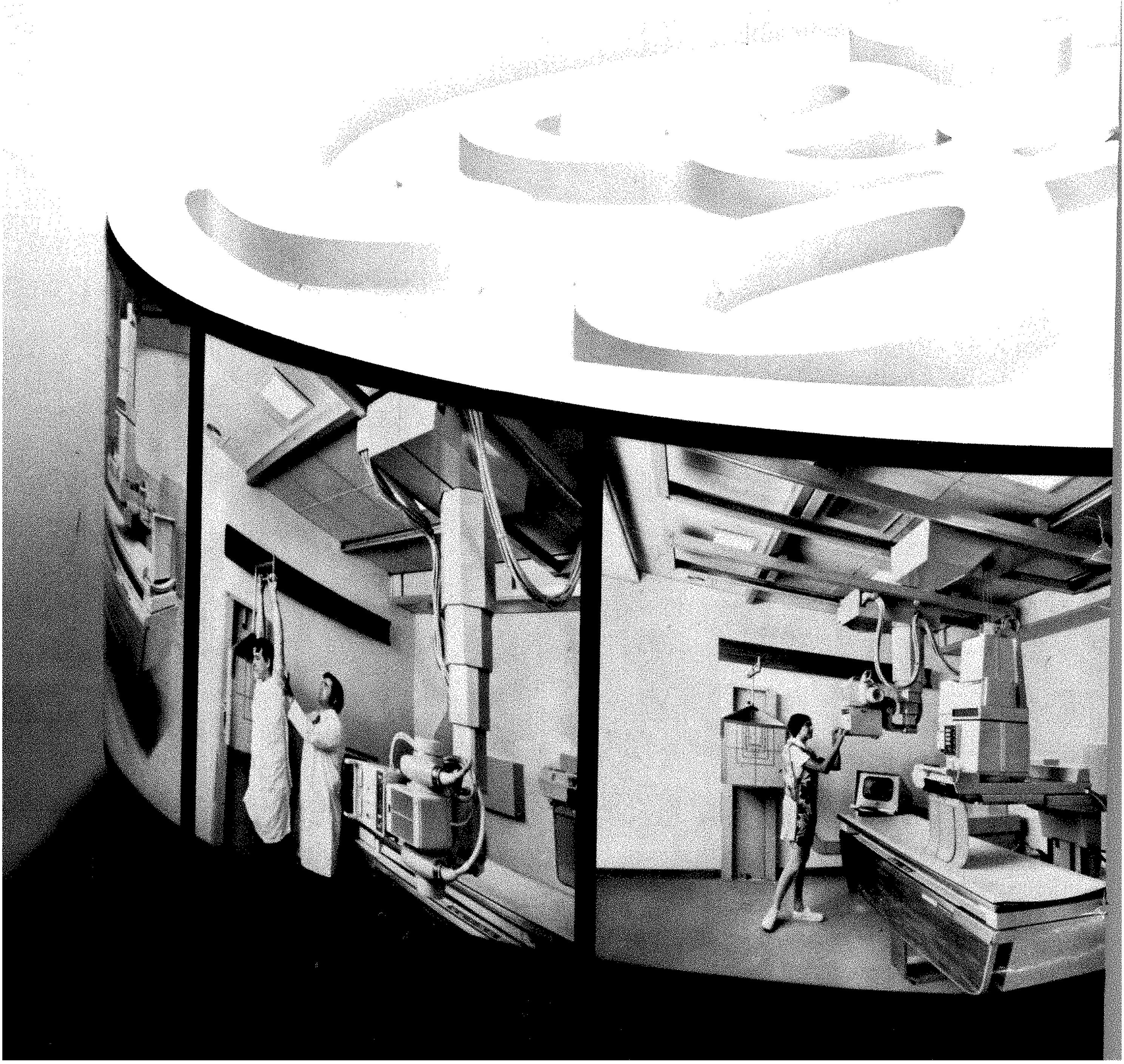

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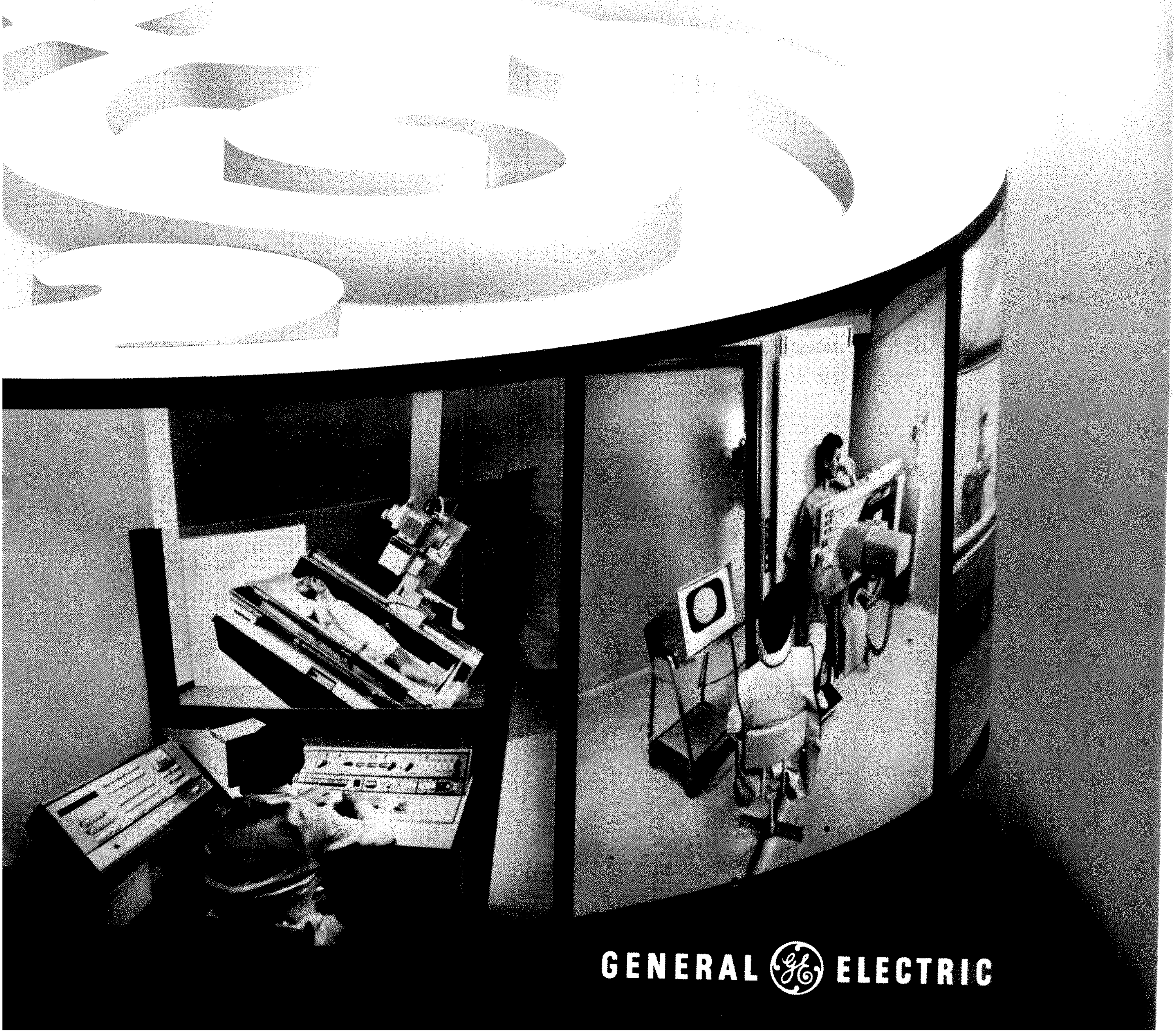

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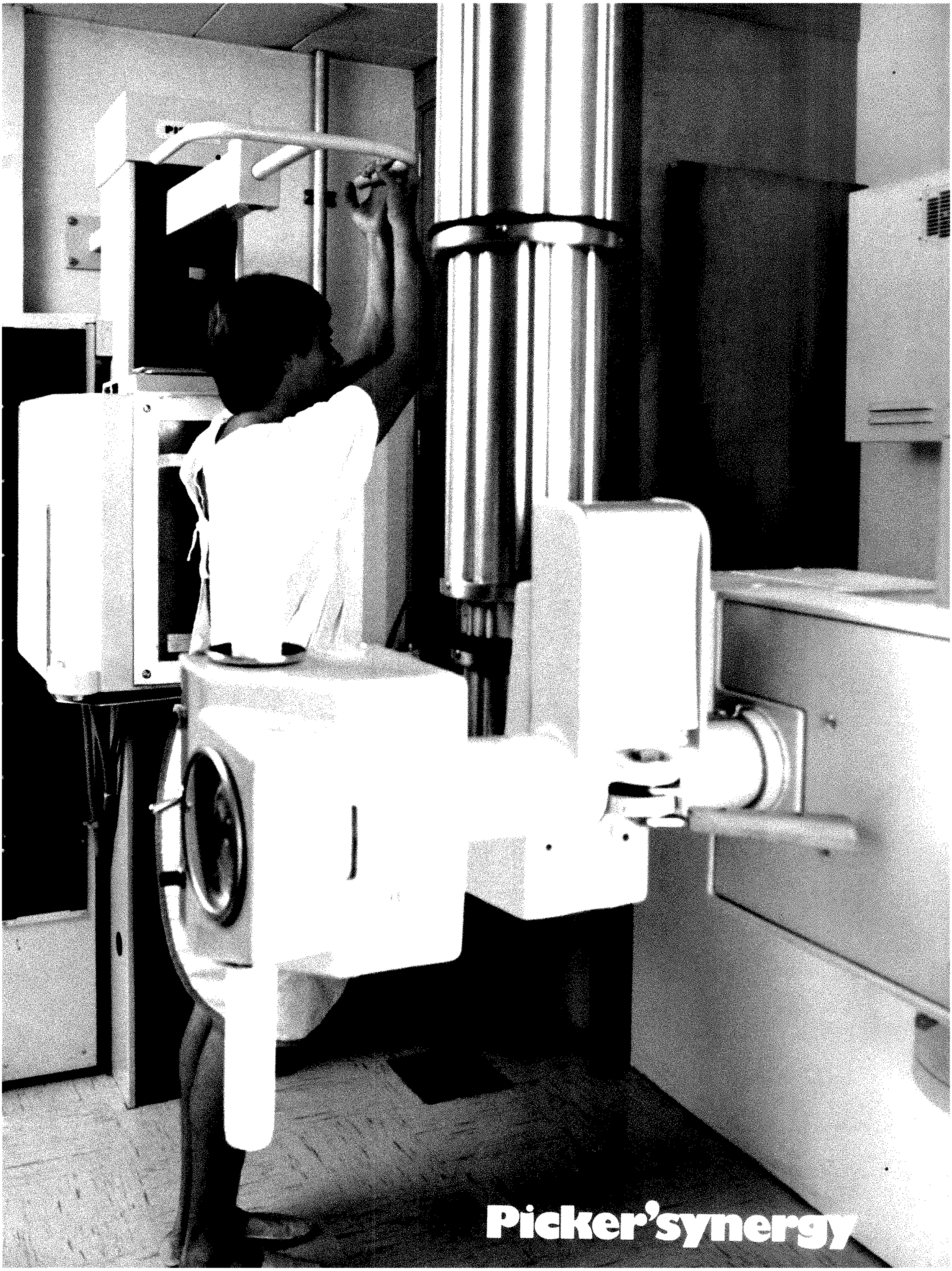

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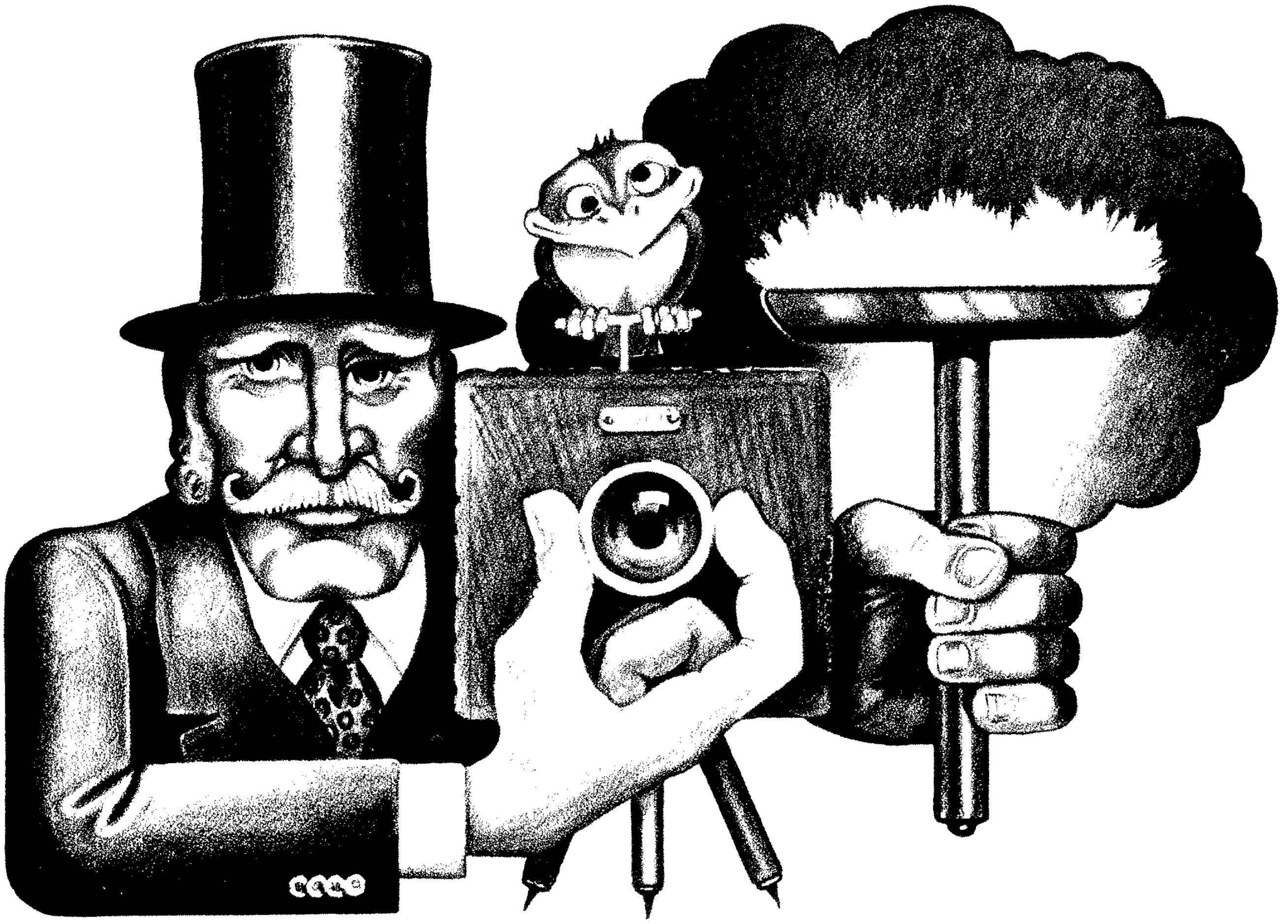

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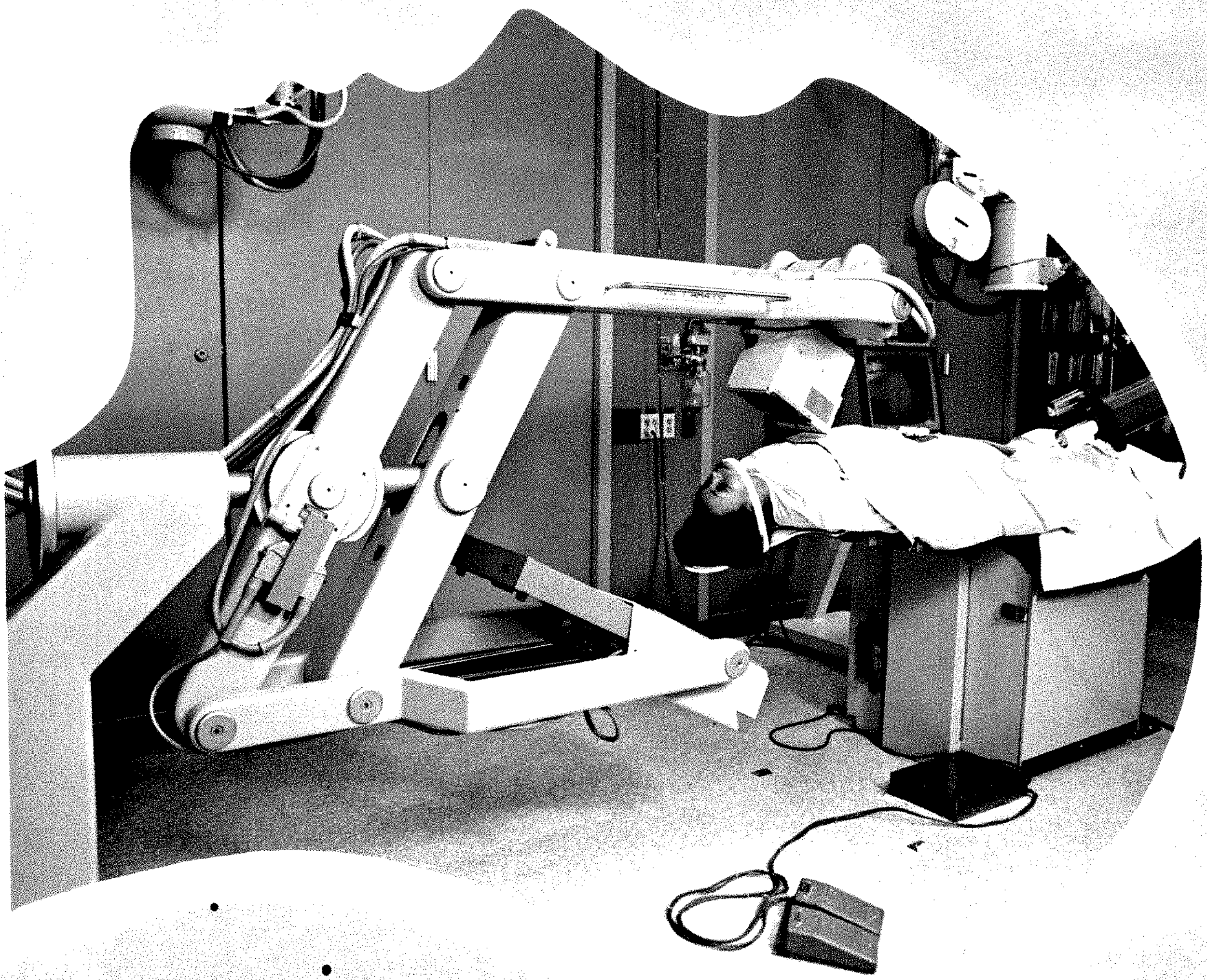

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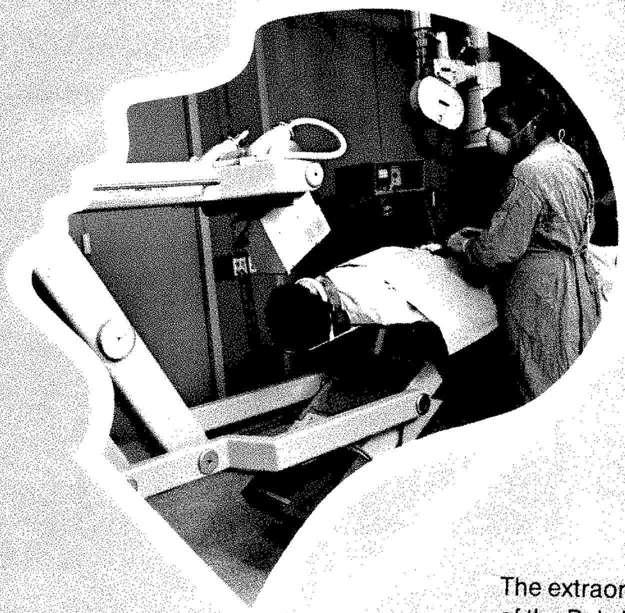

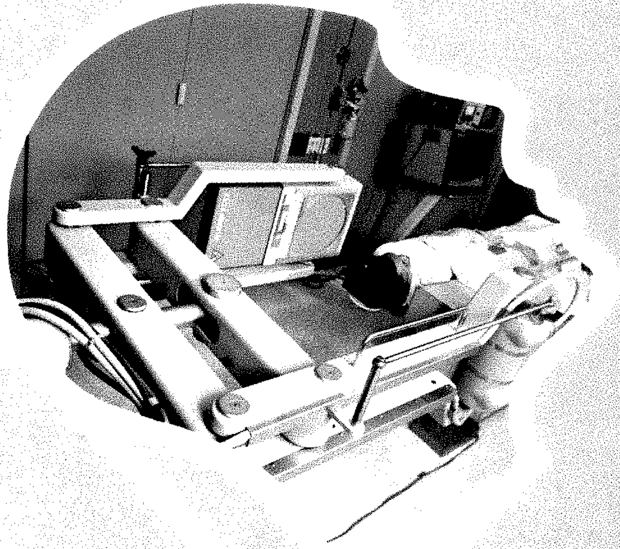

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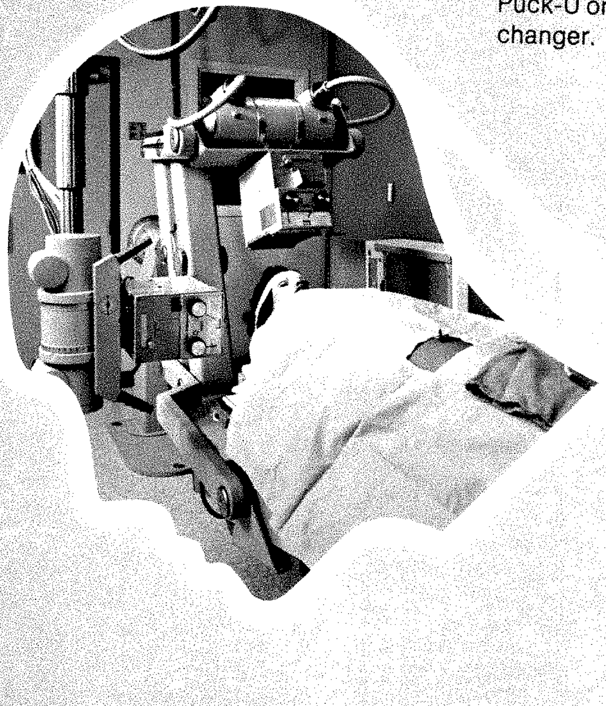

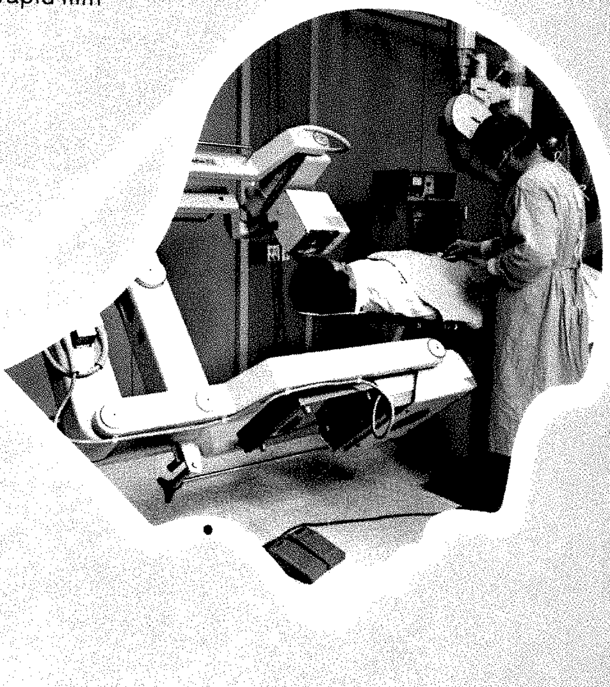

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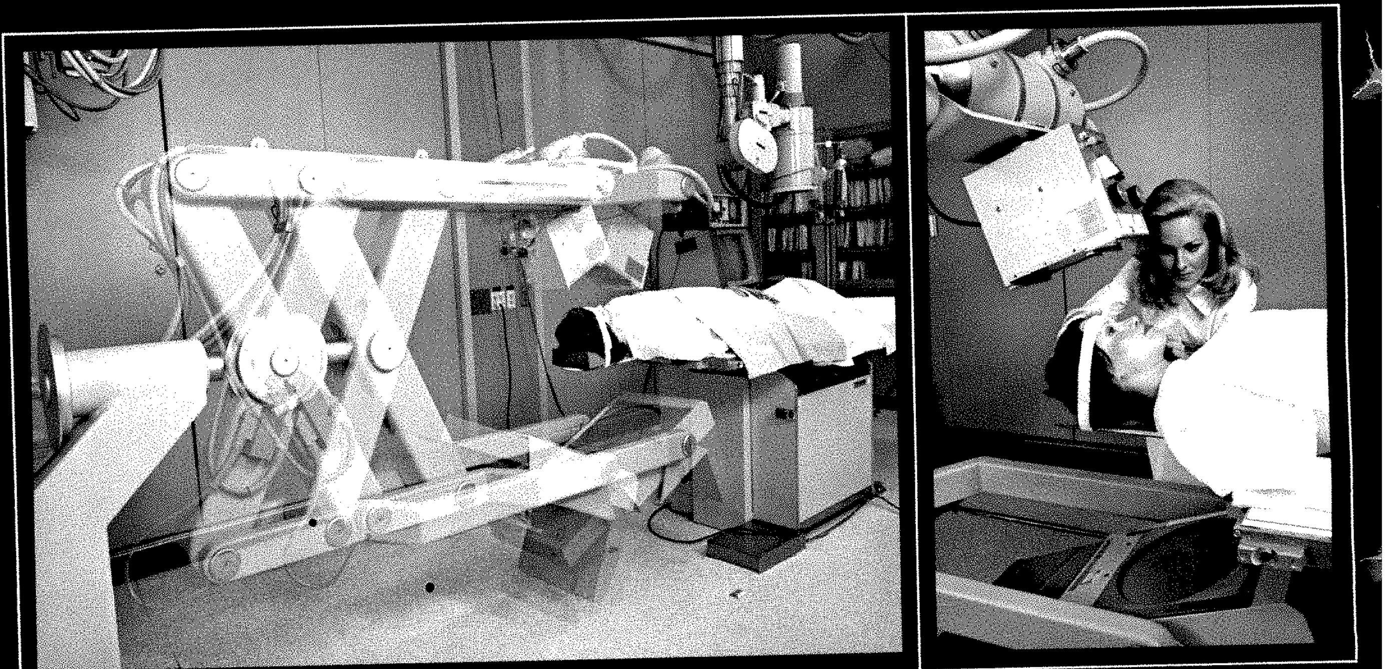

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ELEMENTS OF RADIATION PROTECTION *by* **Ronald V. Scheele** *and* **Jack Wakley,** *both of the Univ. of Virginia School of Medicine, Charlottesville.* Information in this textbook includes atomic structure, ionizing radiation, interaction of radiation with matter, sources of radiation exposure, biological manifestations of radiation exposure, permissible dose limits, principles of radiation protection and monitoring devices. Several chapters of the book deal with federal performance standards and Atomic Energy Commission regulations. The material content and mode of presentation are clear and nonmathematical for those students who have little background in physics and mathematics. *'75, 112 pp., 15 il., 10 tables, $7.95, paper*

THE HAND ATLAS *by* **Moulton K. Johnson** *and* **Myles J. Cohen,** *both of UCLA, Los Angeles, California.* This atlas portrays the anatomy of the hand as the surgeon will encounter it in the operating room – layer by layer, beginning with the skin and ending with x-ray studies of the bones. Photographs of dissections of unembalmed specimens provide more realistic illustrations, all of which are approximately life-size, except where otherwise indicated. Topics include the distal volar forearm, the palm, thumb, fingers, the radial side of the hand, spaces of the hand and wrist mechanics. *'75, 108 pp. (8 1/2 x 11), 121 il. (8 in color), $22.00*

THE PHYSICS OF RADIOLOGY (3rd Ed., 3rd Ptg.) *by* **Harold Elford Johns** *and* **John Robert Cunningham,** *both of the Univ. of Toronto, Toronto, Ontario, Canada.* The emphasis of this Third Edition has been shifted from 200 kv and caesium 137 radiation toward higher energy radiations. Computers are used more frequently in calculations of dose distributions in radiotherapy; therefore, numerous sections devoted to computer techniques have been added. A section has also been added dealing with the solid state dosimeter lithium fluoride. Also introduced are the concepts of kerma, particle fluence and energy fluence and these concepts are illustrated with examples. *'74, 812 pp. (6 3/4 x 9 3/4), 398 il., 92 tables, $24.75*

A STUDY GUIDE IN NUCLEAR MEDICINE: A Modern Up-to-Date Presentation *compiled and edited by* **Fuad Ashkar, August Miale, Jr.** *and* **William Smoak,** *all of the Univ. of Miami, Miami, Florida. (22 Contributors)* A comprehensive review of nuclear medicine is provided by this book which is a necessity for persons studying for the examination of the American Board of Nuclear Medicine. Covered are such topics as interaction of gamma rays with matter, control of radiation exposure to man, basic mathematics of nuclear medicine, electrolytes and body composition, essentials of rectilinear scanning, cardiovascular imaging and treatment of thyroid disease with radioiodine. *'75, 488 pp., 312 il., 44 tables, cloth-$22.75, paper-$17.50*

"TRAUMA" AND "NO-TRAUMA" OF THE CERVICAL SPINE *edited by* **Kenneth R. Kattan,** *Univ. of Cincinnati College of Medicine, Cincinnati, Ohio. (11 Contributors)* This book, written with the radiologist, the orthopedic surgeon and the neurosurgeon in mind, includes all types of trauma of the cervical spine and the diseases that predispose cervical spine trauma. The chapter on "no-trauma" describes the conditions which resemble trauma. Also presented are how to recognize cervical spine trauma. In one chapter different traumas are described in detail, while other chapter topics include the roentgenographic follow-up, the pediatric patient, non-trauma cases, and trauma in the diseased spine. *'75, 328 pp., 292 il., $24.50*

INDICATIONS AND ALTERNATIVES IN X-RAY DIAGNOSIS: A Guide to the Effective Employment of Roentgenologic Studies in the Solution of Diagnostic Problems (2nd Ed.) *by* **Melvyn H. Schreiber,** *Univ. of Texas Medical Branch, Galveston.* This illustrated volume describes and depicts the various kinds of roentgenologic examinations available for the unravelling of diagnostic problems. It is divided into chapters based upon organ systems with common abnormalities illustrated. Emphasis is on providing the reader with a thorough background in the uses to which the ordinary and special x-ray studies may be put. *'74, 192 pp., 98 il., $11.50, paper*

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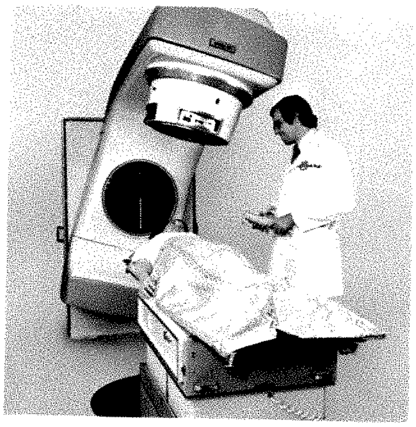

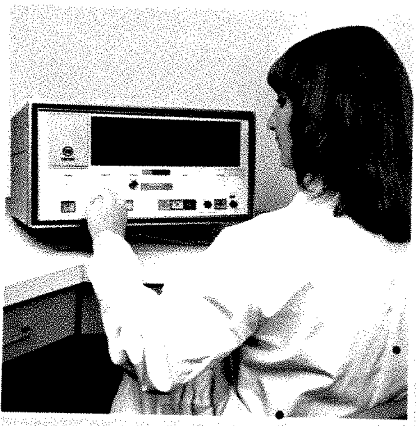

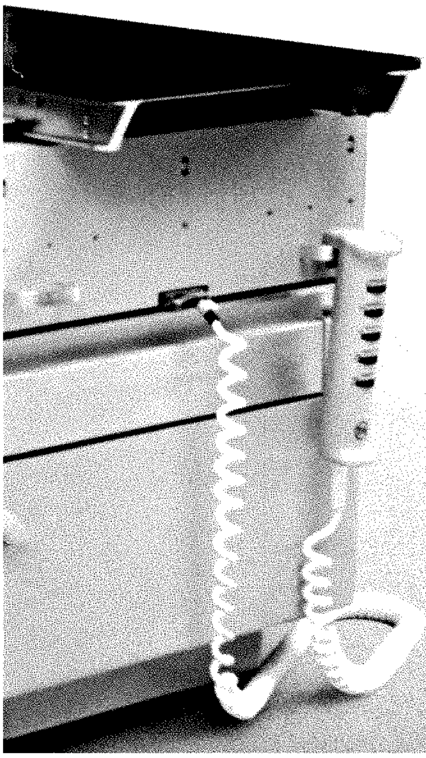

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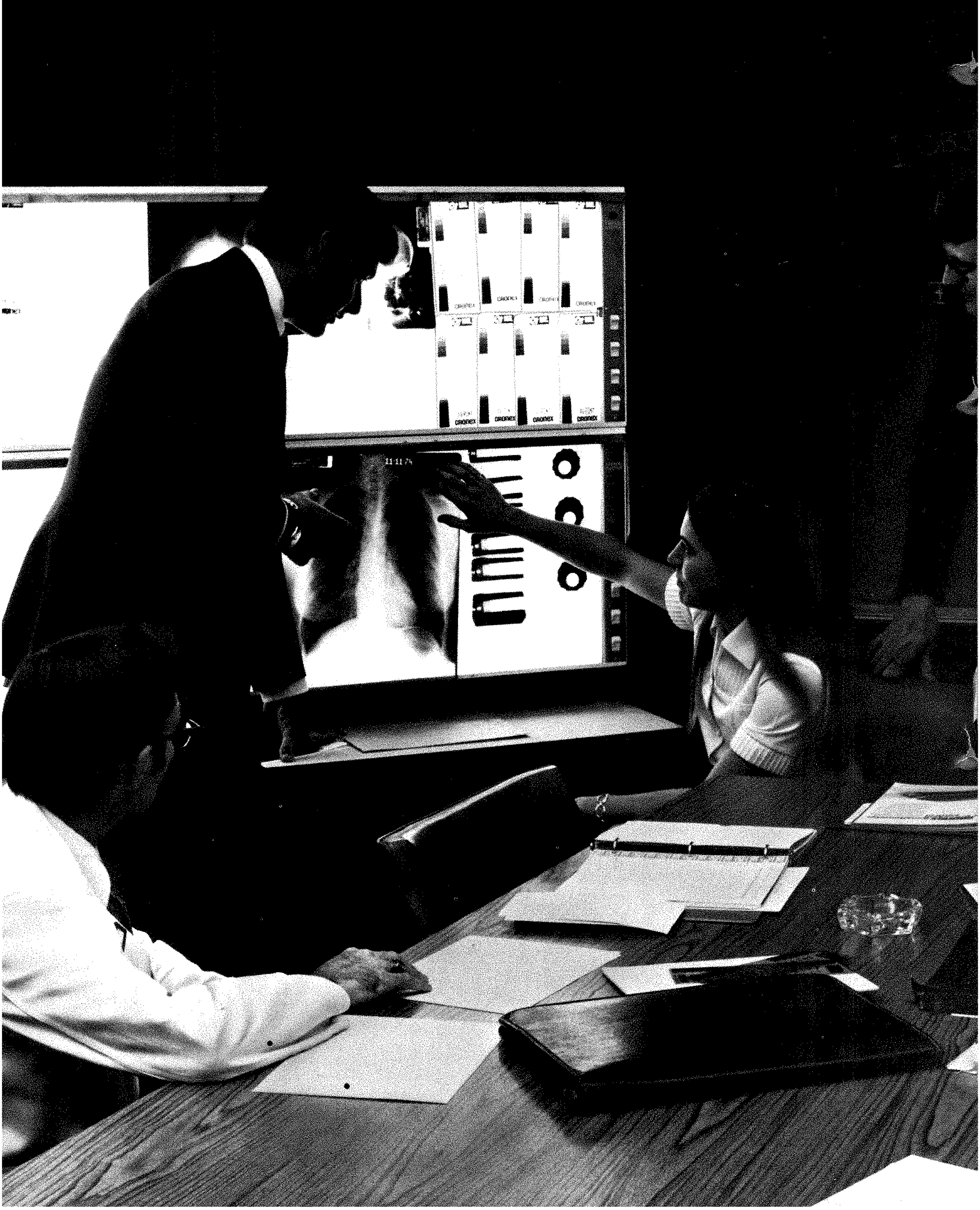

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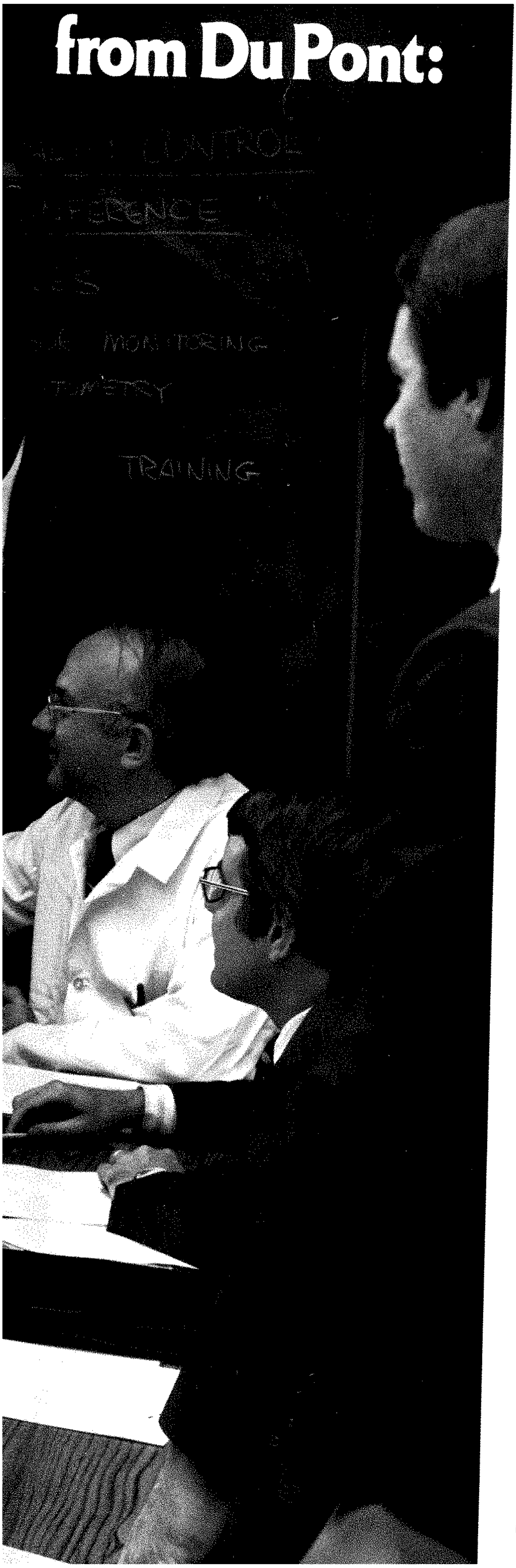

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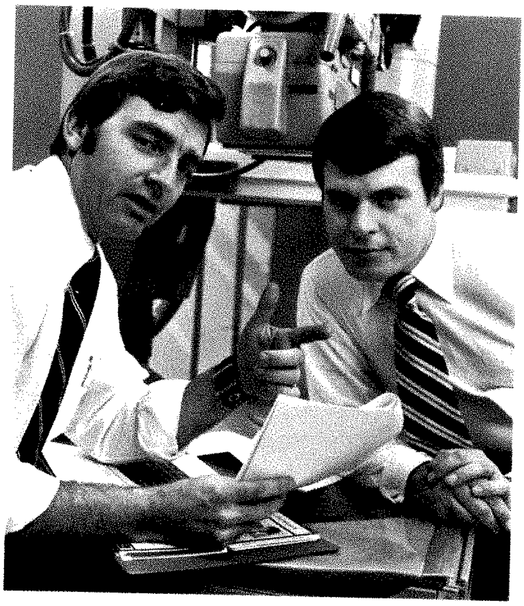

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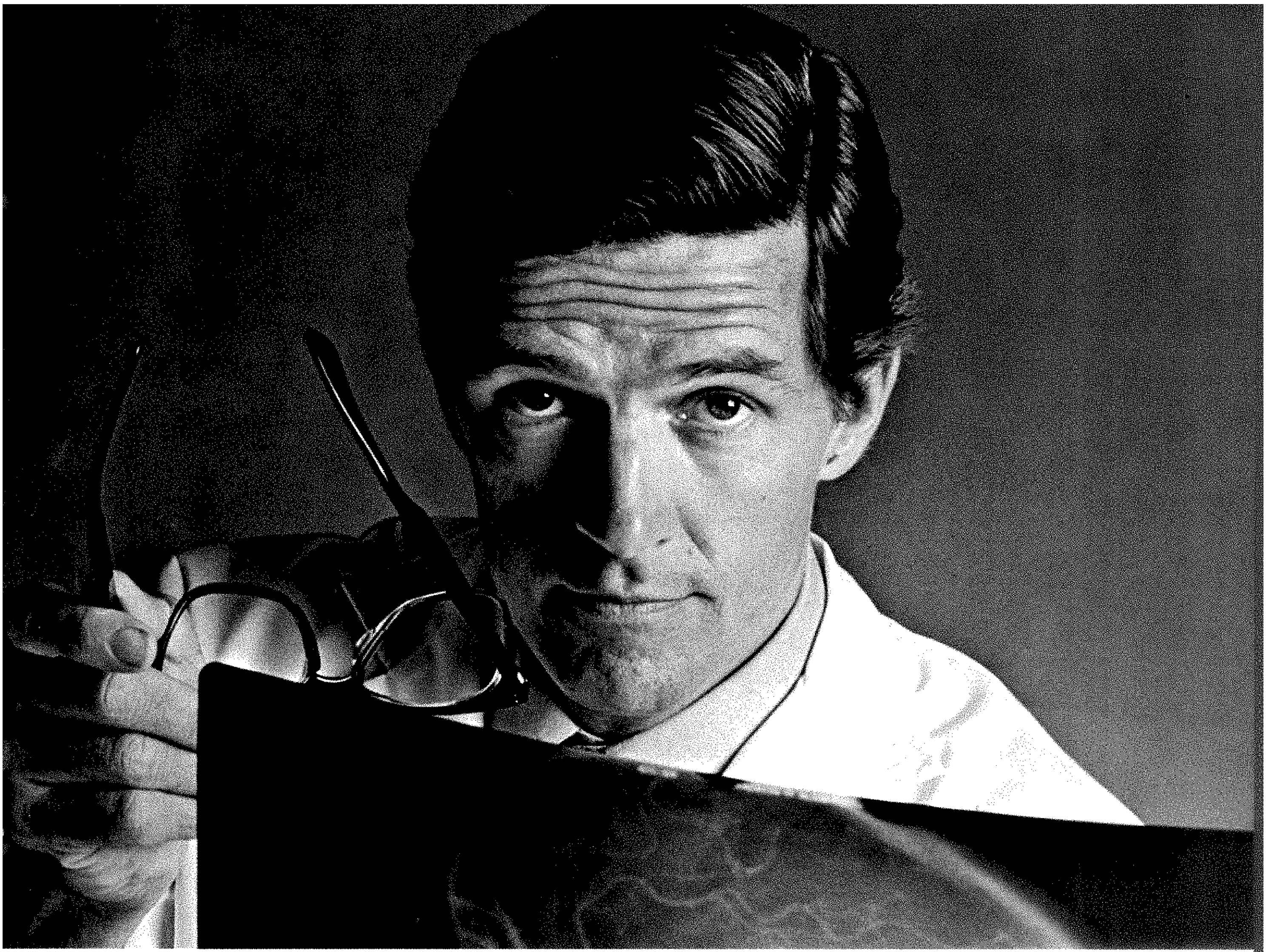

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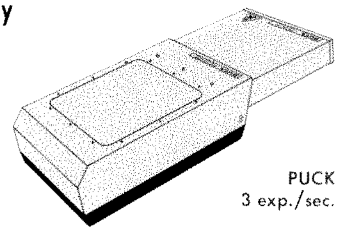

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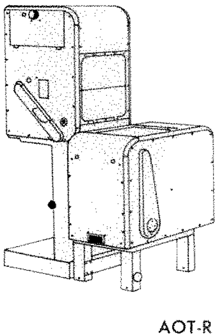

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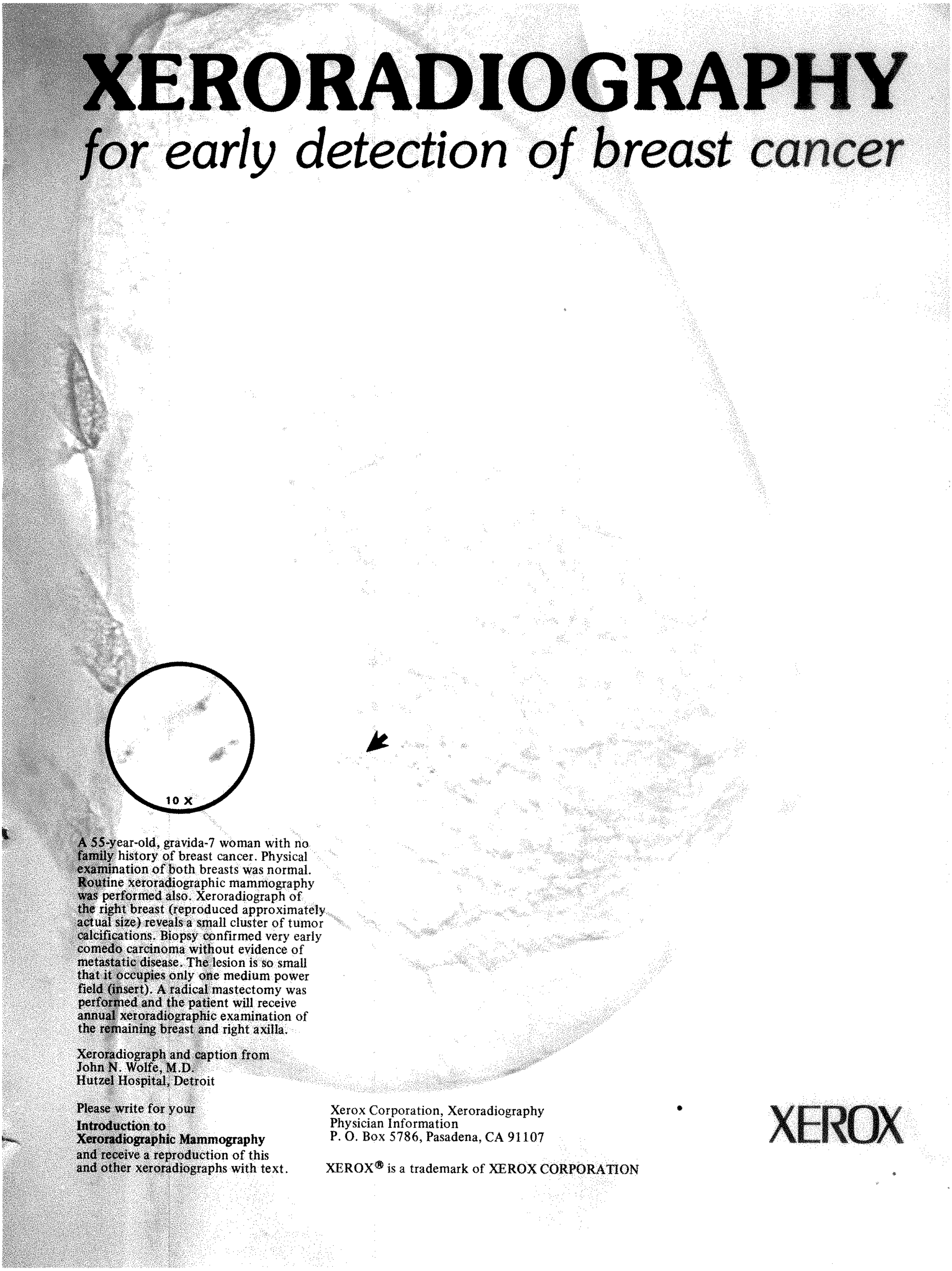

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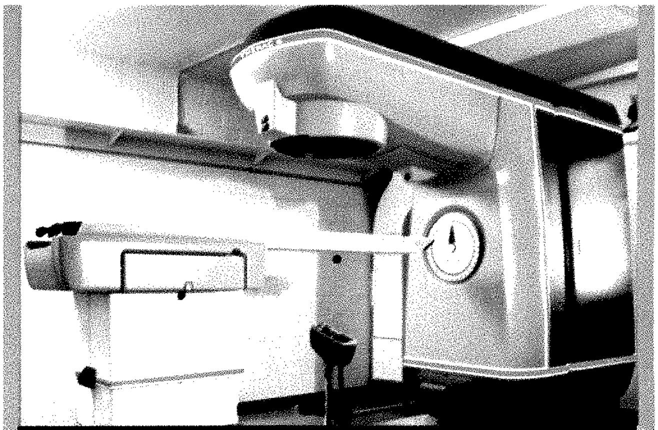

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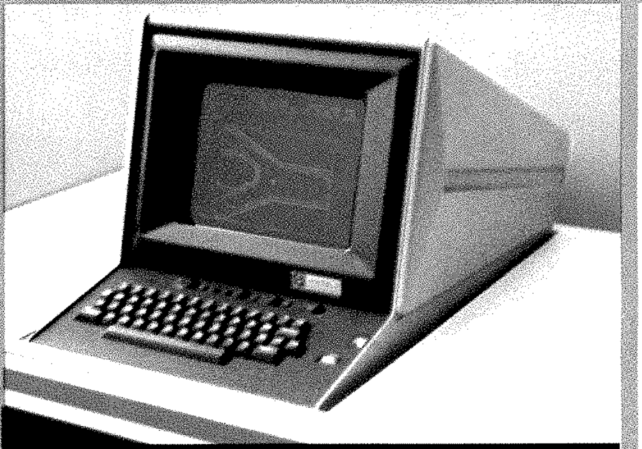

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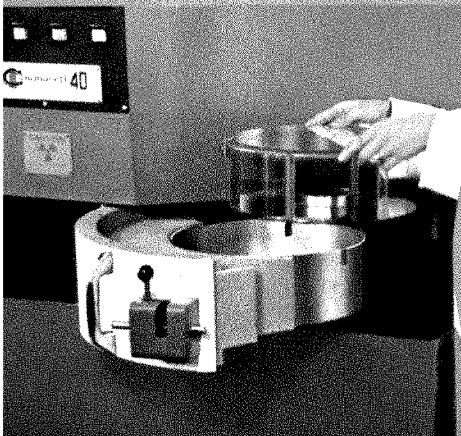

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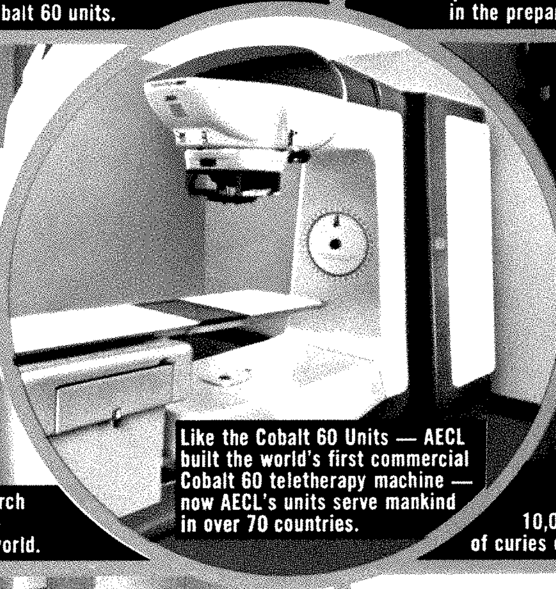

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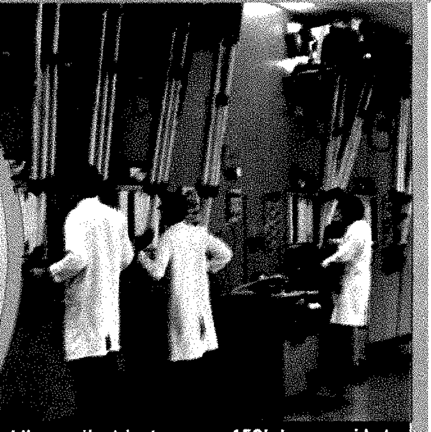

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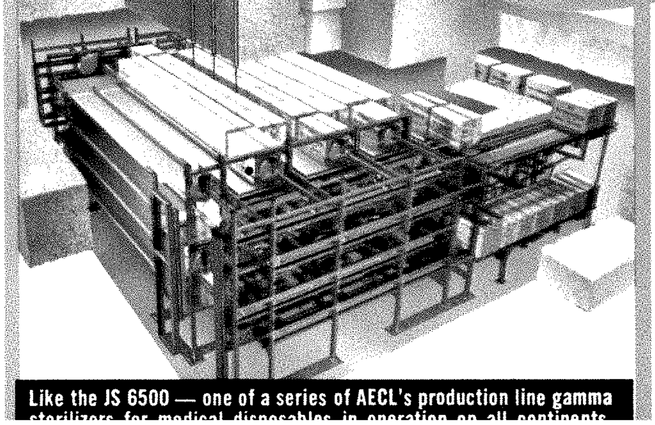

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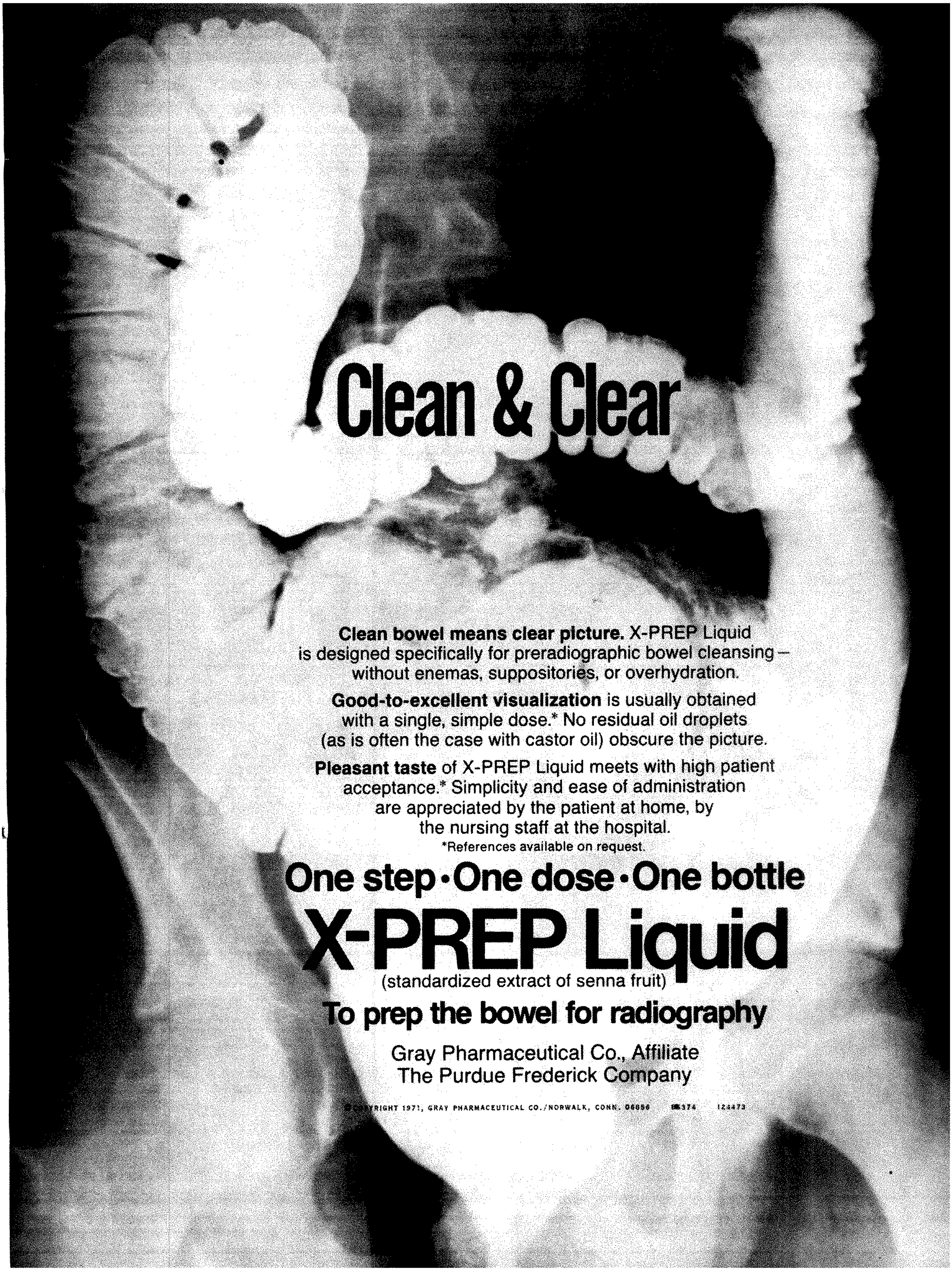

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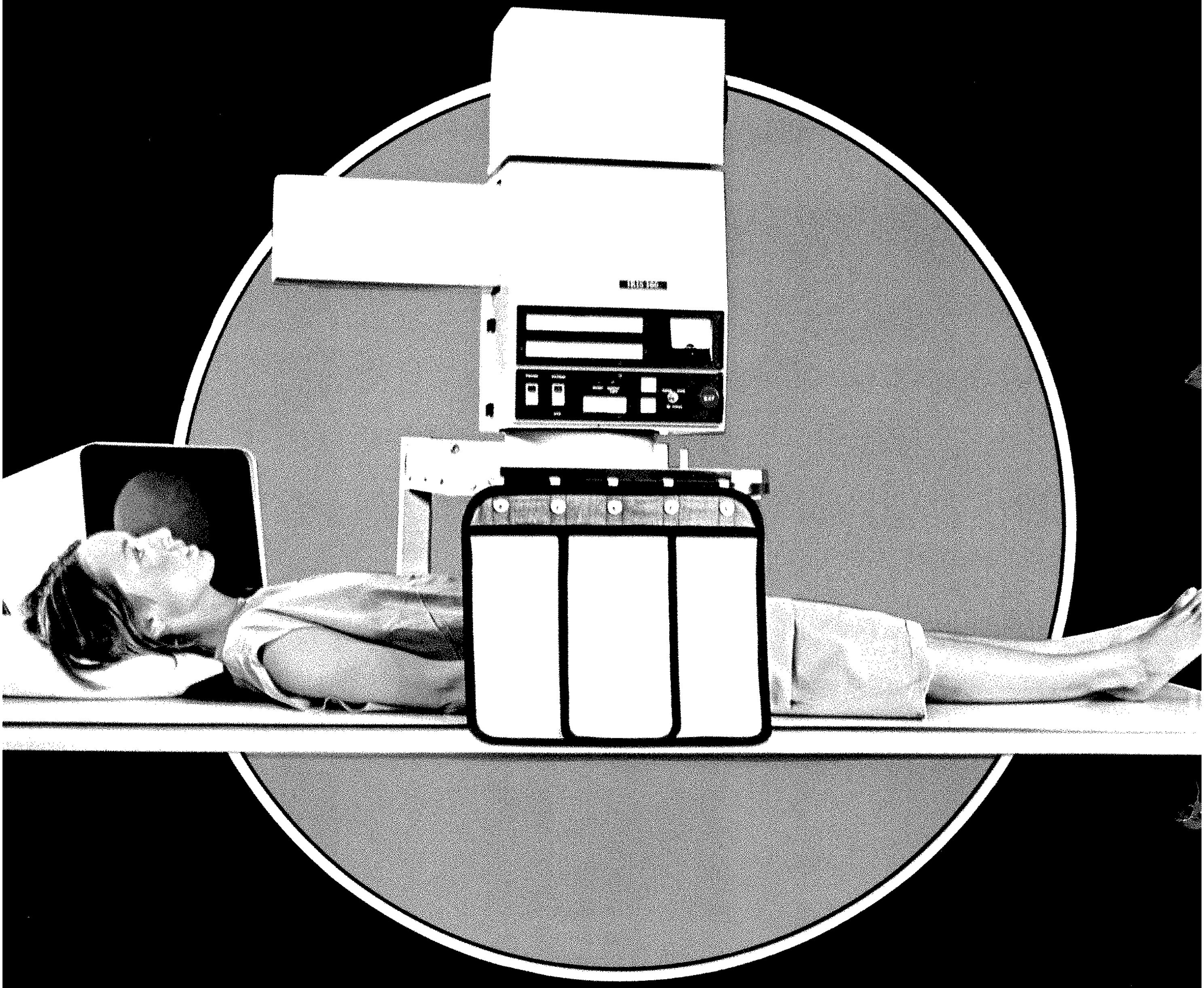

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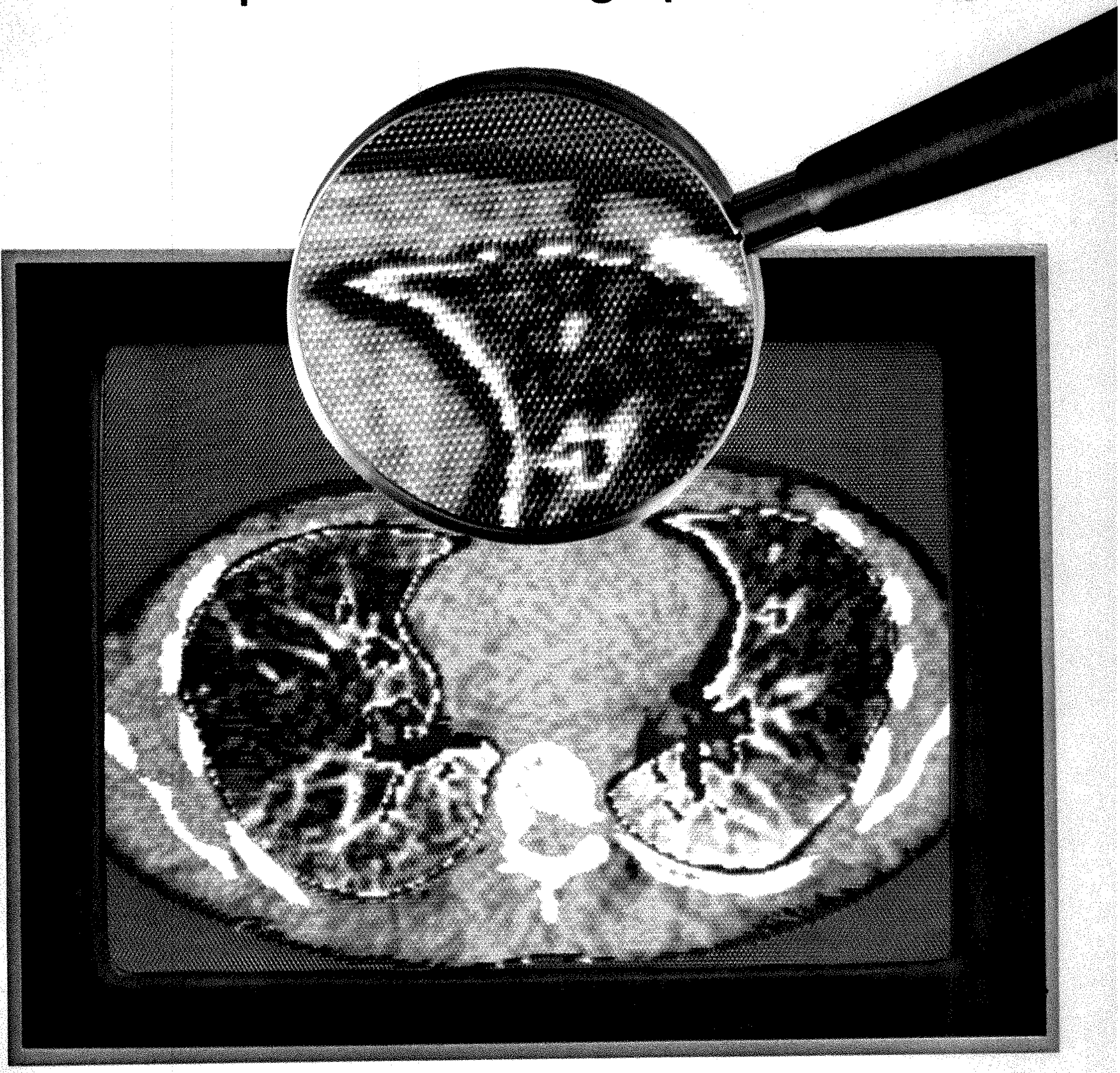

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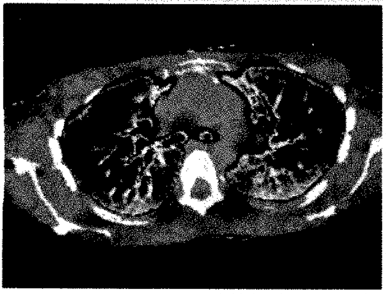

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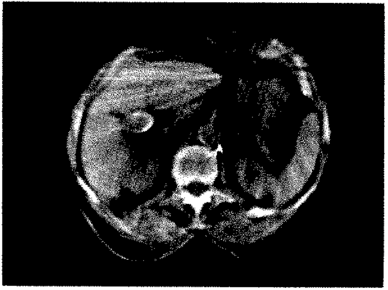

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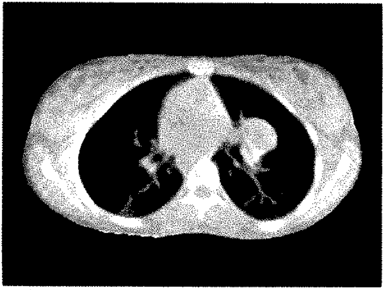

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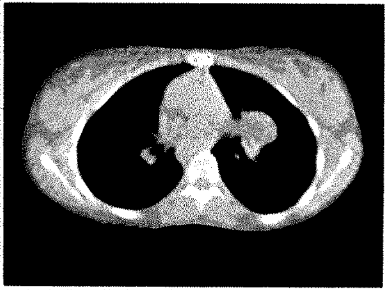

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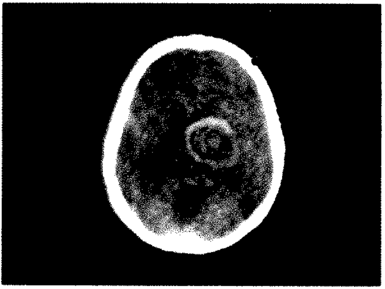

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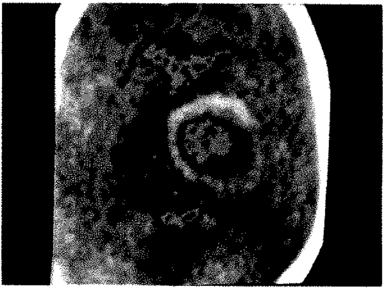

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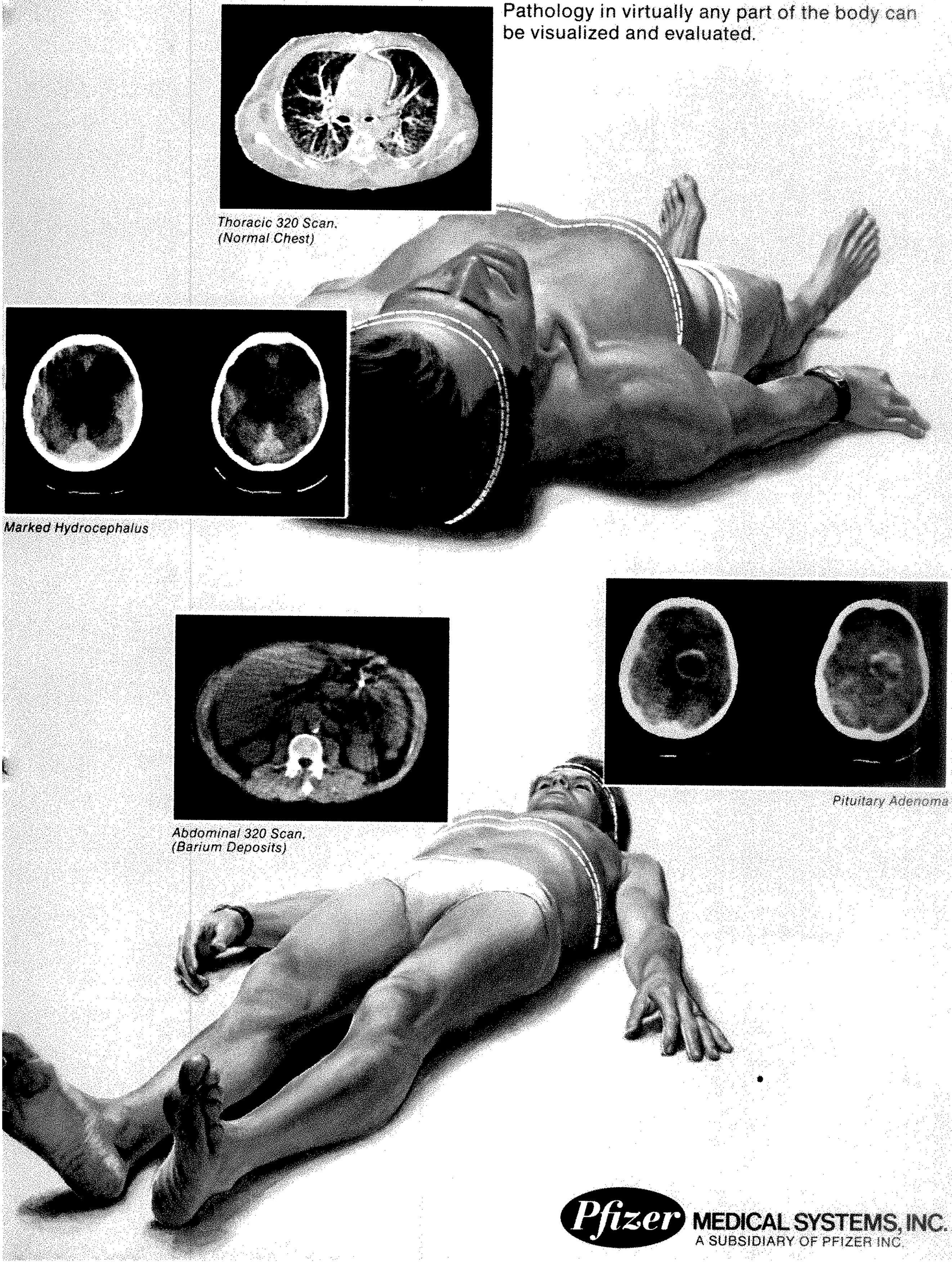

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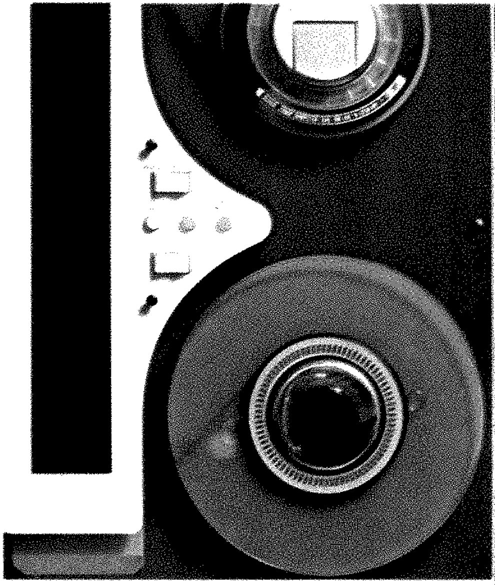
WHOLE BODY COMPUTERIZED TOMOGRAPHIC SCANNER

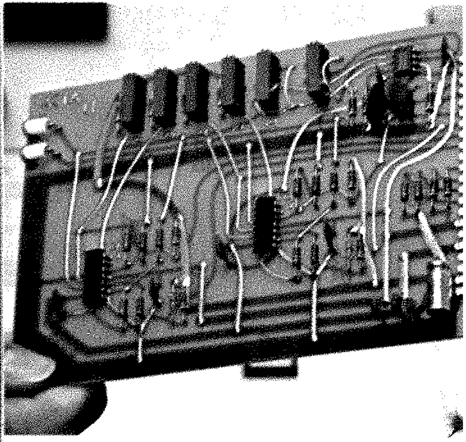
A revolutionary innovation in diagnostic radiology maintained by an original concept of service...and backed by the full resources of a great medical organization

The Pfizer Medical Systems Field Engineer is an integral component of the ACTA-Scanner Service Program.

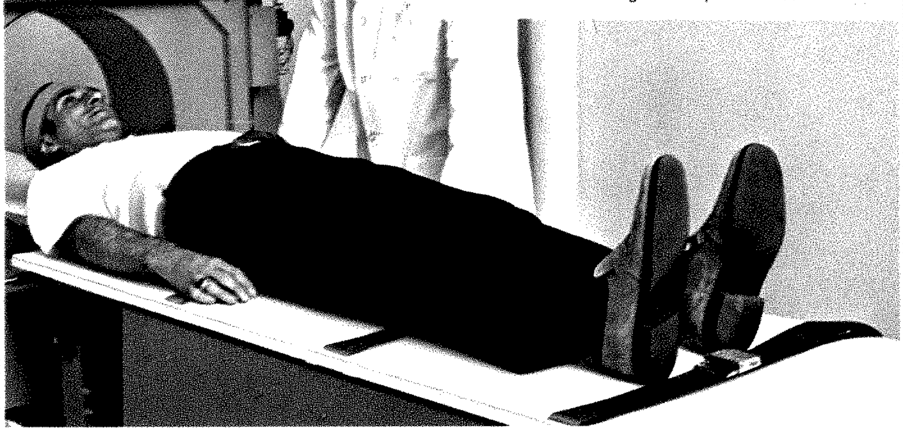
Field engineer readily available



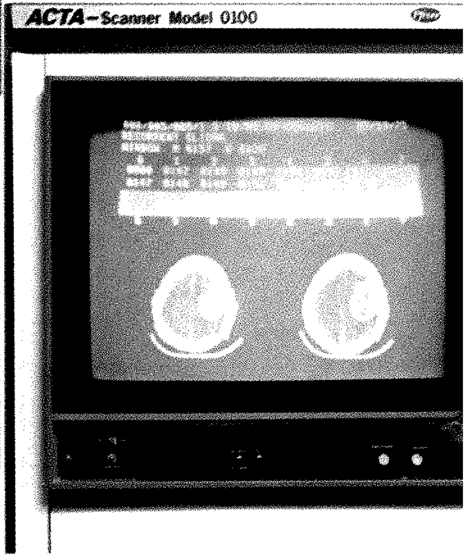
All data stored on magnetic tape for future recall



Replacement parts, if needed, are readily available

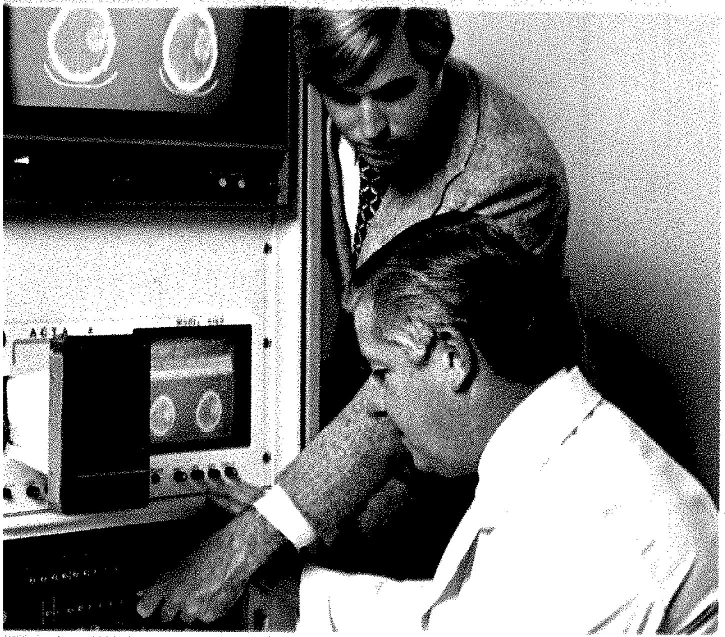


Minimal patient preparation before scan

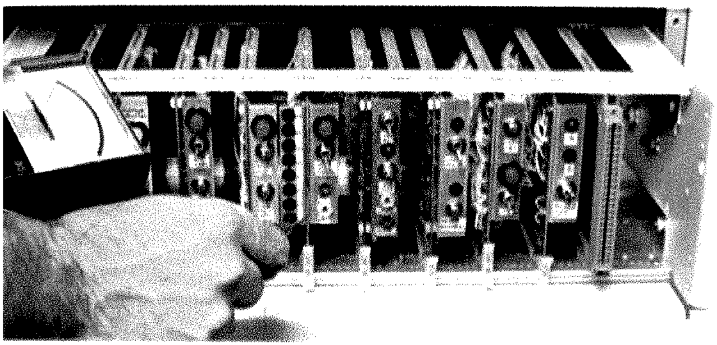


Instant display following completion of scan

COLLEGE OF MEDICINE
LIBRARY



eld engineer provides continued updating on capabilities



equent visits by field engineer keep ACTA-Scanner at peak performance

Automation with Representation

A team of highly qualified field engineers is on standby duty to respond to your needs within two hours, if necessary.

Warranty: Any necessary maintenance can be done at night or during nonpeak hours, as designated. No charges for all parts and service support during normal working hours.

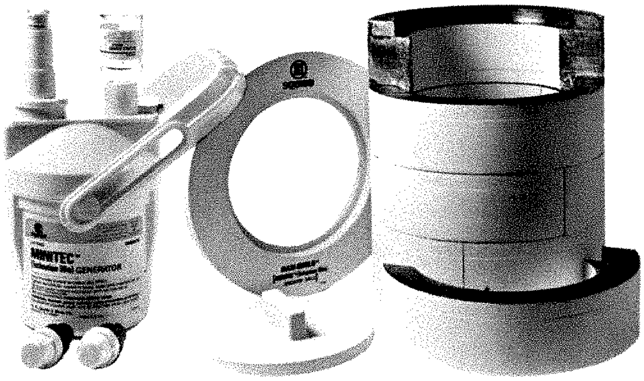
Continuous inspection: Frequent visits, at your convenience, will be made to assure optimum performance.

Direct link to research and development: Your representative will keep you apprised of the activities of the Pfizer physicists and x-ray and computer experts who are dedicated to providing ever greater performance and more features on your ACTA-Scanner.

Pfizer MEDICAL SYSTEMS, INC.
A SUBSIDIARY OF PFIZER INC.

WHAT'S NOW SQUIBB?

On the current nuclear medicine scene



MINITEC® (Technetium 99m) Generator

The Technetium 99m Generator using fission product molybdenum to produce technetium 99m. MINITEC is unlike any generator you've ever used—made small to make sense.

Designed for easy handling

- MINITEC has its own handle for easy lifting, easy carrying and reduced hand exposure
- Weighs only 24½ lbs., less than 5" in diameter, under 8½" high

Designed for easy elution

- Sets up in seconds
- Elutes in only 3 minutes after eluent vial has emptied

Designed for safety

- No exposed tubing when eluting
- 1⅝" lead surrounds the MINITEC column
- 1½" of extra lead protection from MAXI-SHIELD™. Base, cap and interlocking half rings easily assembled on site . . . only the cap is removed for elution. (You get MAXI-SHIELD free with your first MINITEC Generator purchase.)

Designed for convenience

- MINITEC Generator is available in 50,100, 200, 300, 400 and 500 mCi potencies. Delivery on Monday AM (precalibrated through Thursday) and Wednesday (precalibrated through Monday) provides maximum versatility to satisfy technetium requirements of your lab's work load.

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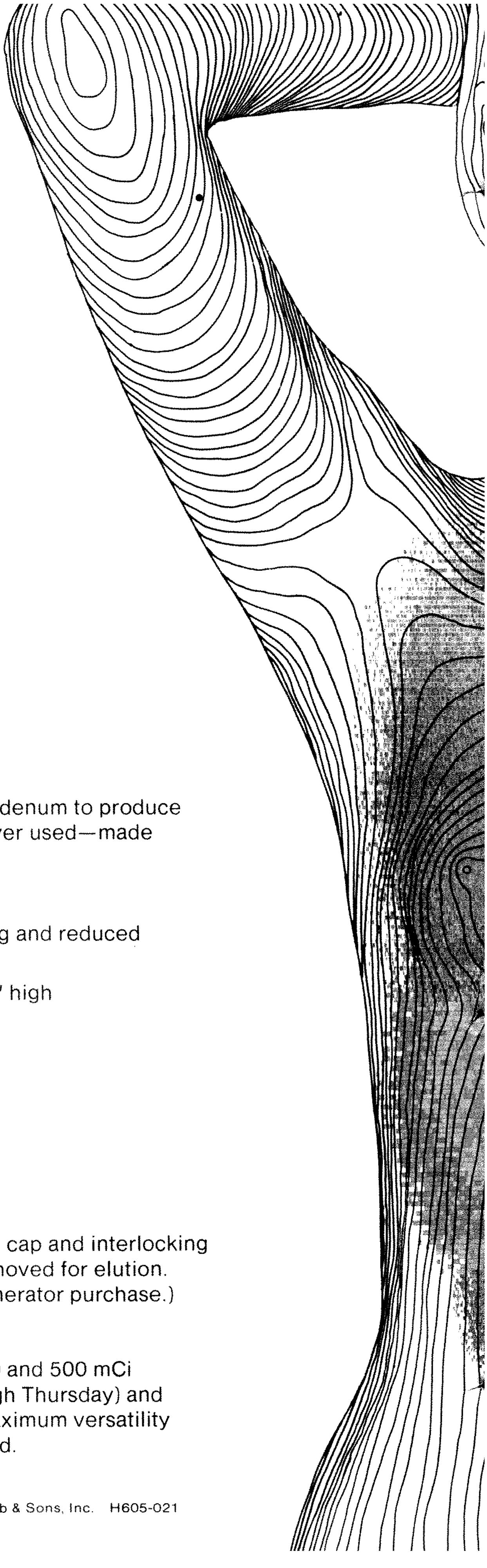
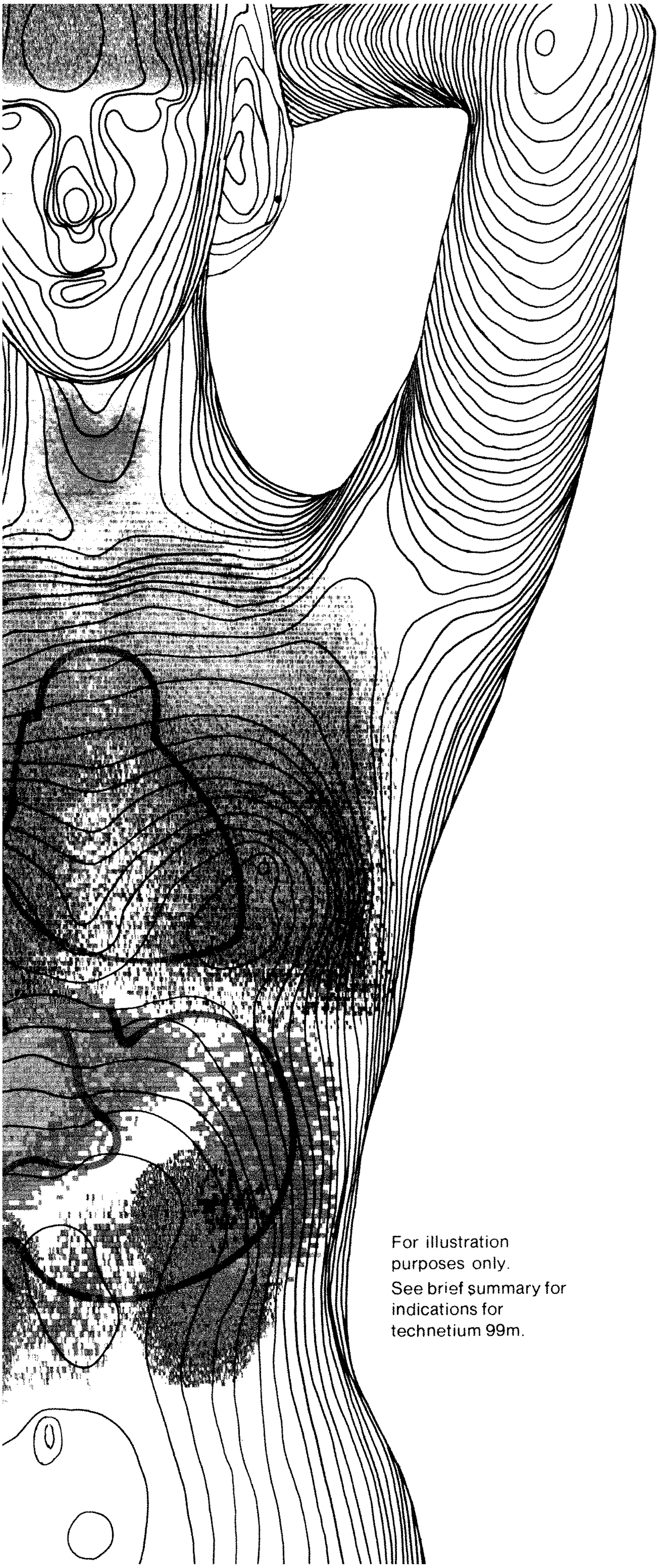




For illustration
purposes only.

See brief summary for
indications for
technetium 99m.

Minitec®
(Technetium 99m)
Generator

Minitec® (Technetium 99m) Generator provides a means of obtaining a sterile, non-pyrogenic supply of technetium 99m (^{99m}Tc) as sodium pertechnetate ^{99m}Tc.

Indications: Sodium pertechnetate ^{99m}Tc is indicated for brain imaging, thyroid imaging, salivary gland imaging, blood pool imaging, and placenta localization.

Contraindications: At present, there are no known contraindications to the use of sodium pertechnetate ^{99m}Tc.

Warnings: Radiopharmaceuticals should be used only by physicians who are qualified by specific training in the safe use and safe handling of radionuclides, produced by nuclear reactor or cyclotron, and whose experience and training have been approved by the appropriate federal or state agency authorized to license the use of radionuclides.

This radiopharmaceutical should not be administered to women who are pregnant or who may become pregnant or during lactation unless the information to be obtained outweighs the possible potential risks from the radiation exposure involved. Ideally, examinations using radiopharmaceuticals, especially those elective in nature, of a woman of childbearing capability should be performed during the first few (approximately 10) days following the onset of menses.

Since radioactive pertechnetate is secreted in milk during lactation, formula-feedings should be substituted for breast-feedings.

Important: Since material obtained from the generator may be intended for intravenous administration, aseptic technique must be strictly observed in all handling. Only the eluent provided should be used to elute the generator. Do not administer material eluted from the generator if there is any evidence of foreign matter.

Precautions: As in the use of any other radioactive material, care should be taken to insure minimum radiation exposure to the patient consistent with proper patient management and to insure minimum radiation exposure to occupational workers.

At the time of administration, the solution should be crystal clear.

Adverse Reactions: At present, adverse reactions have not been reported following the use of sodium pertechnetate ^{99m}Tc.

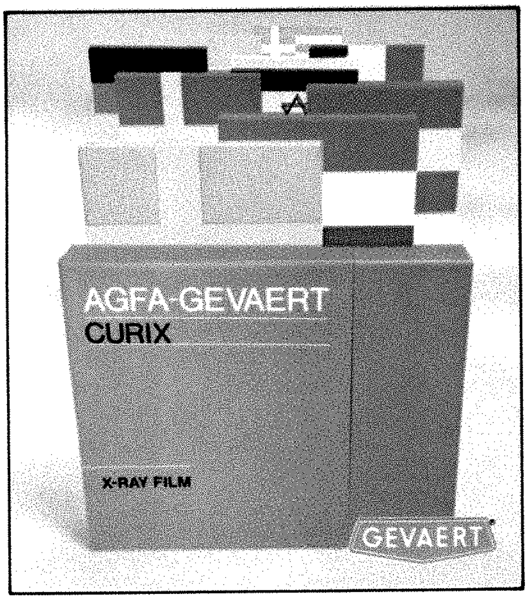
For complete prescribing information, consult package insert.

How Supplied: Minitec (Technetium 99m) Generator is available in potencies of 50, 100, 200, 300, 400, and 500 mCi. Supplied with the generator are vials of eluent containing 5 ml. of a sterile, non-pyrogenic solution of 0.9% sodium chloride in water for injection. Also supplied is suitable equipment for eluting, collecting, and assaying the technetium 99m.

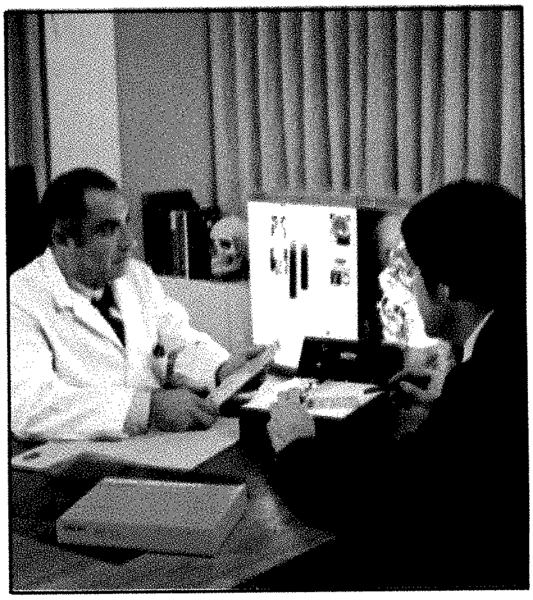
Medotopes®

SQUIBB HOSPITAL DIVISION
E. R Squibb & Sons, Inc.
Princeton, N.J. 08540

Global leader Agfa-Gevaert introduces a completely new film– CURIX RP-1

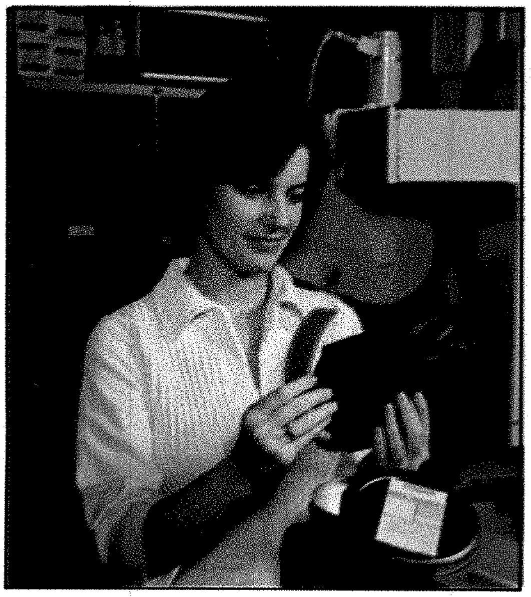


Agfa-Gevaert is world renowned for its leadership in x-ray film research, development, and advanced quality control systems. CURIX RP-1 is a new generation x-ray film for all your general diagnostic needs. Unsurpassed image fidelity provides excellent contrast and low fog for maximum visualization.



Agfa-Gevaert also means highly experienced technical/processor service. Skilled professionals analyze your requirements, and provide personalized assistance in controlling techniques and processing parameters vital to maintaining departmental quality control.

backed by a total X-Ray technical service program



Agfa-Gevaert makes a full range of films for special procedures. Each is formulated and packaged to accommodate the particular requirements of special procedures equipment designed for cardiovascular and neurological radiographic examinations.

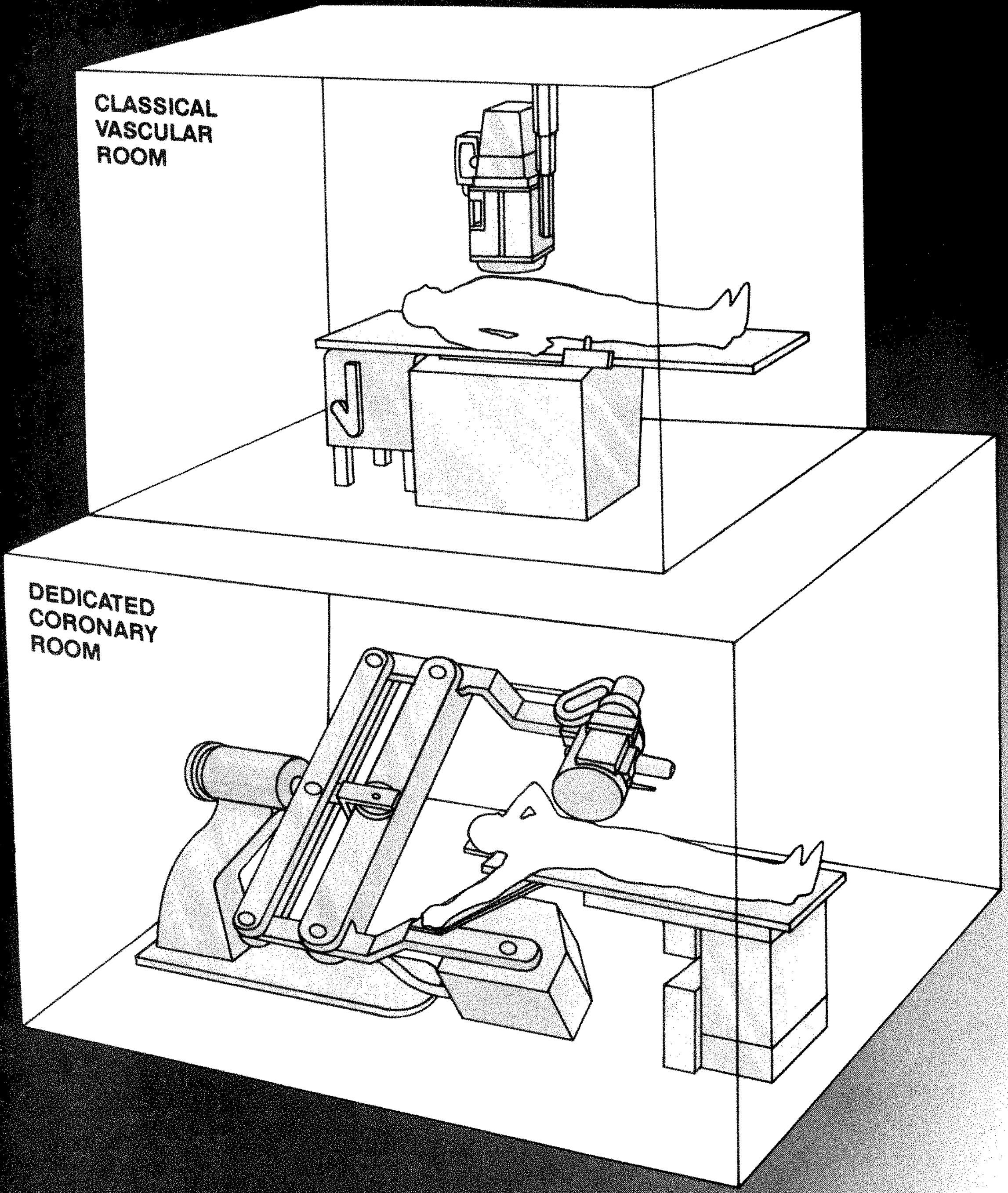
Agfa-Gevaert offers excellent economy through direct sales and delivery by LOW X-RAY, their nationwide distributor. Technical support, including periodic maintenance and repair of automatic processors, as well as a complete line of accessories and supplies are all available from your local service center.

LOW X-RAY

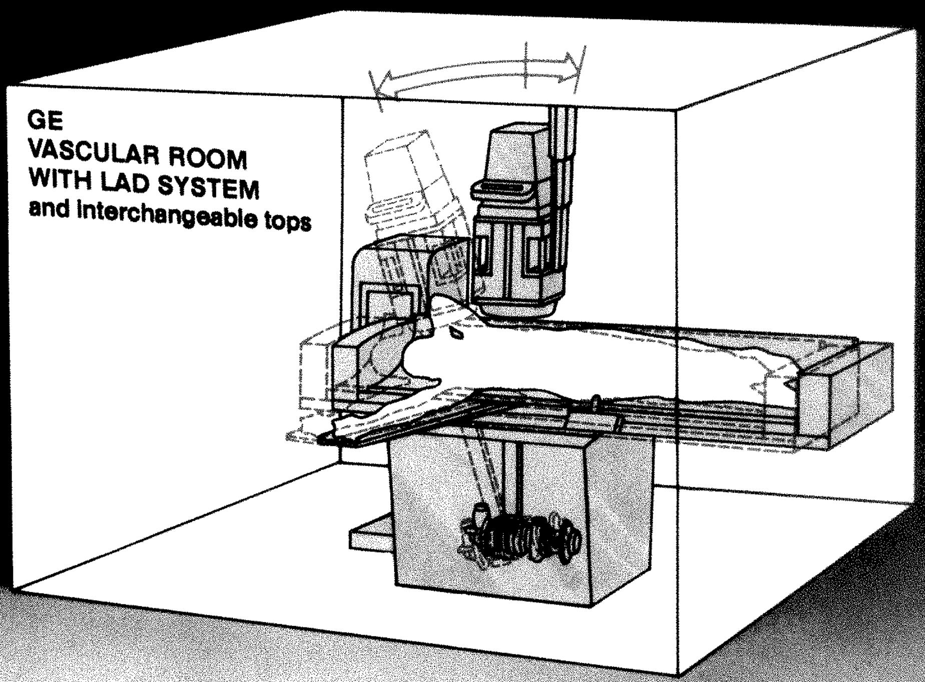
A Division of IPCO Hospital Supply Corporation
1025 Westchester Avenue
White Plains, New York 10604

2245

Why two rooms...



when one does it all?



With the LAD system, you can perform all angiographic procedures in one room – even get the axial projection of the Left Anterior Descending coronary artery.

GE's new LAD system gives you dedicated results without the need for a separate dedicated system. The unique design features an angulating tube and intensifier with detachable linkage, combined with a rotating patient cradle. As a result, LAD performs all standard vascular procedures plus dedicated coronary arteriography. You get the uncompromised image quality of the Fluoricon® 300, with cine and/or 105 mm recording. And cradle top design minimizes filtration, enhancing film clarity.

Versatility — One room handles all procedures, including visceral, peripheral, cardiological and neurological exams. LAD even allows biplane oblique ventriculography, not possible with a U-arm.

Economy — Minimum investment, maximum capability. LAD can be installed at a fraction of the cost of a cumbersome U-arm. LAD attaches to conventional vascular equipment, minimizing space needs.

Rigidity — Minimal overhang of LAD system avoids the "tuning fork" shake of U-arms. LAD retains the rigidity of a classical vascular system.

Positioning ease — Tube and intensifier angulation are automatically synchronized. Just pull the intensifier forward and it automatically angulates to the desired projection. Film changers remain in position for cine and large film recording. No undesirable repositioning of equipment or patient. Easy patient accessibility in case of emergency.

Operator safety — Minimized radiation, with primary beam shielded by lead-lined table base.

Find out how the LAD system can give your GE vascular procedures room total angiographic capability at minimum cost. Talk to your GE representative.

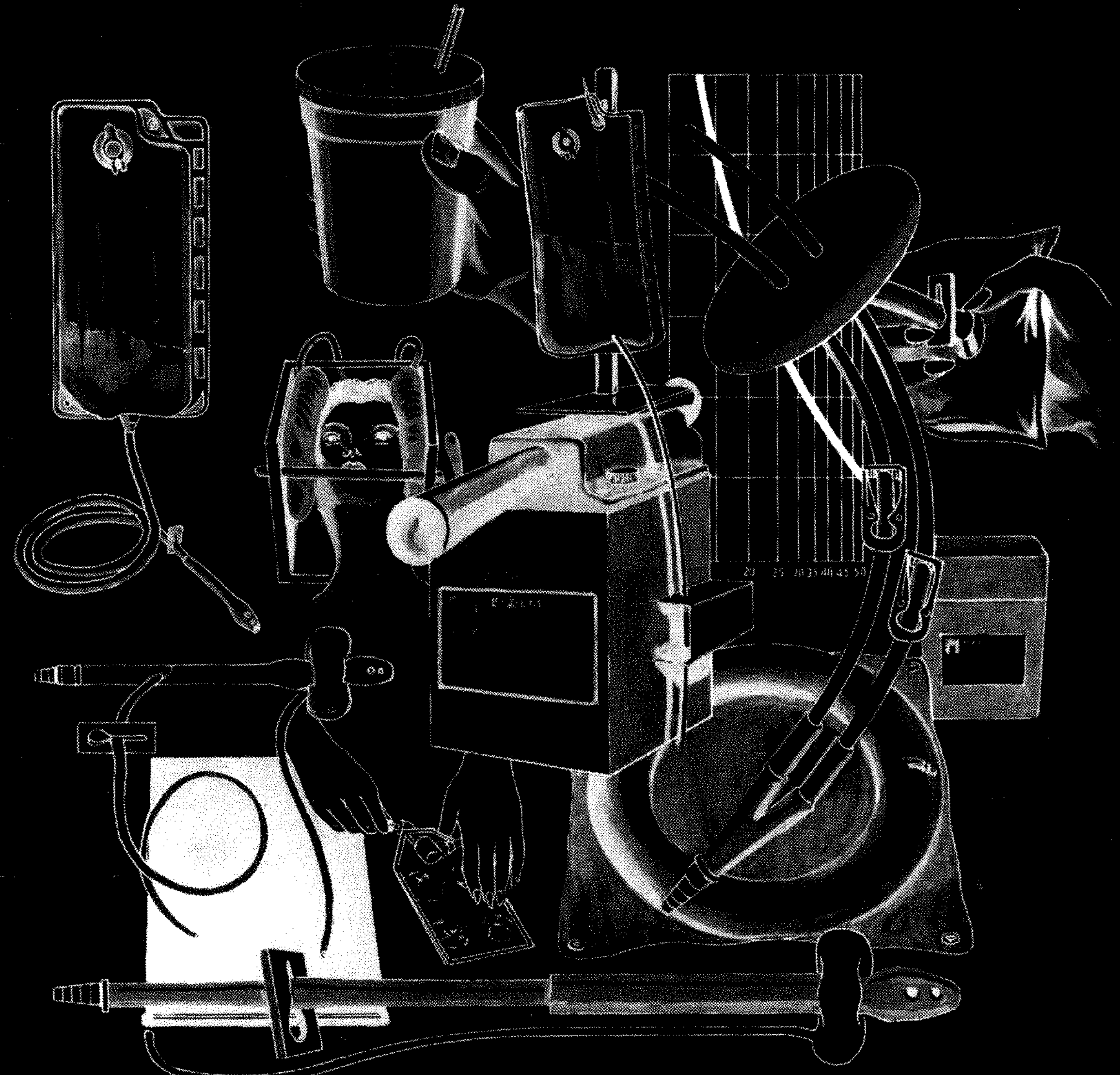
General Electric Medical Systems,
Milwaukee, Toronto, Madrid.

LAD system gives you a lot of room.

GENERAL ELECTRIC

Barium, Barium Systems, and Ancillary Products

...formulated and designed to meet the realistic needs of the Modern Radiology Department



E-Z-EM

System of your choice

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Westbury, N.Y. 11590 (516) 333-8230

International Affiliates: E-Z-EM Rooster B. V., Infirmeriestraat 6-8, Rotterdam 16, Netherlands
E-Z-EM De Mexico, S. A. de C. V., Calz. Azcapotzalco La Villa No 882, Zona Industrial Vallejo, Mexico 16 D. F.

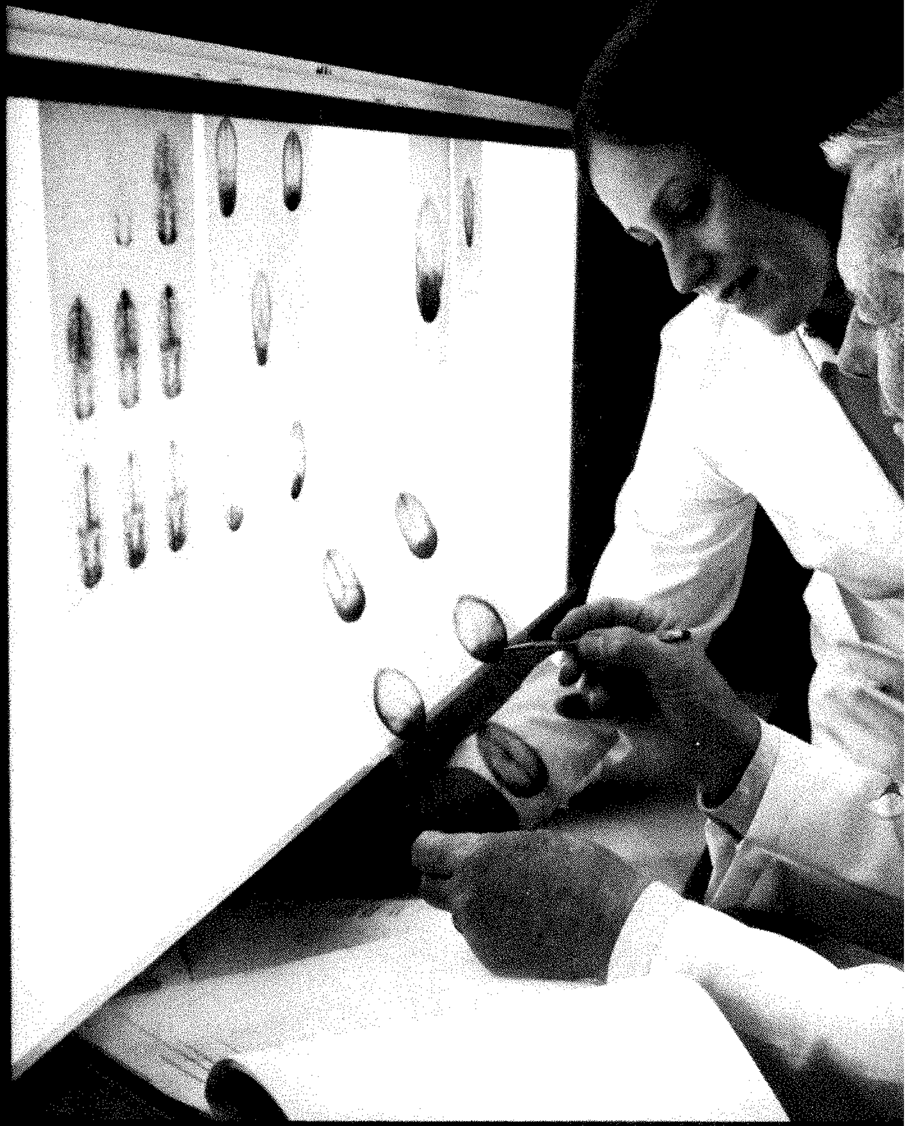
Quality is what Kodak is all about.

It goes a long way toward providing consistent imaging results. Quality is the heart of our products. The ingredient of our services. The extra advantage of the skilled counsel of our technically experienced representatives who can meet your radiographic requirements.

Quality is the Kodak expertise in imaging technology which can be of value to you because diagnostic decisions can sometimes depend on the quality of the diagnostic image.

When what you want is image quality, consider Kodak quality... **where can we help you most?**

Your concern is
Ours is meeting your
with Kodak quality.



Focus on KODAK Medical X-ray Films.

To meet your varied imaging requirements, Kodak offers a wide range of quality films. Each is designed to consistently provide well-defined diagnostic information on the viewbox—where quality images count.

Films for general radiography. Whether you need a high-contrast film for maximum detail or a wide-latitude film to record variations in tissue densities, Kodak has them. If speed is your concern, use our high-speed films to shorten exposure time. Each of our films provides good transport reliability in automatic film-handling equipment.

Films for special technics. In addition to general radiographic needs, you may have other areas where you require consistent image quality. Here you also have a choice of Kodak films: for special procedures; for subtraction; for therapy localization; for cinefluorography; for spot film radiography; and for cathode-ray tube imaging—thermography, ultrasonography, computerized axial tomography.

New Advances in Imaging Technology.

Products for mammography. Compared with any current Kodak film and screen combination for mammography, two new products—Kodak Min-R film and Kodak Min-R screen—offer the fastest speed with equal or better image sharpness.

Rare earth imaging products. Research in rare earth phosphors resulted in Kodak Lanex regular screens and Kodak ortho G film. They provide higher speed—so you can shorten exposure time, or reduce kilovoltage, or decrease milliamperage. All of which can help extend your radiographic technic and equipment capabilities.

making a diagnosis. imaging needs...

Films for nuclear medicine. Kodak offers transparency films for single, multiple, or dynamic imaging. These include Kodak film for nuclear medicine SO-179—ideal for recording images from cathode-ray tube displays. Transparency films resist fading and curling, are easy to

And they can provide high-

processing in 90 or 150 seconds.

Kodak Efficiency Improvers.

Radiographic minification products. Now you can minify radiographs with Kodak Retnar products. The advantages are many: greater ease of filing, faster accessibility, and improved file integrity.

The curved cassette. Kodak X-Omatic cassettes have specially designed, curved covers that force out air when closed, creating an intimate screen/film contact for consistently high image quality. Easy to open and close with one hand. Durable—resists damage, either to the cassette or in the screen/film contact.

The positive patient data

identification camera records data on the radiograph itself, in full room light. No lead letters or numbers to fall off, less chances for misidentification. It's an accurate and efficient means of monitoring patient flow.

Automatic processing. When patient load requires rapid access to processed radiographs, Kodak has a 90-second automatic processor you can depend on. If you need a compact processor for emergency or satellite areas, Kodak has a 150-second automatic processor that uses unheated water, cuts back on costs. Both deliver consistent quality radiographs.

How do you get all this from Kodak? Turn the page...

Having a Kodak TSR who knows your problems, gives you a head start on the answers.

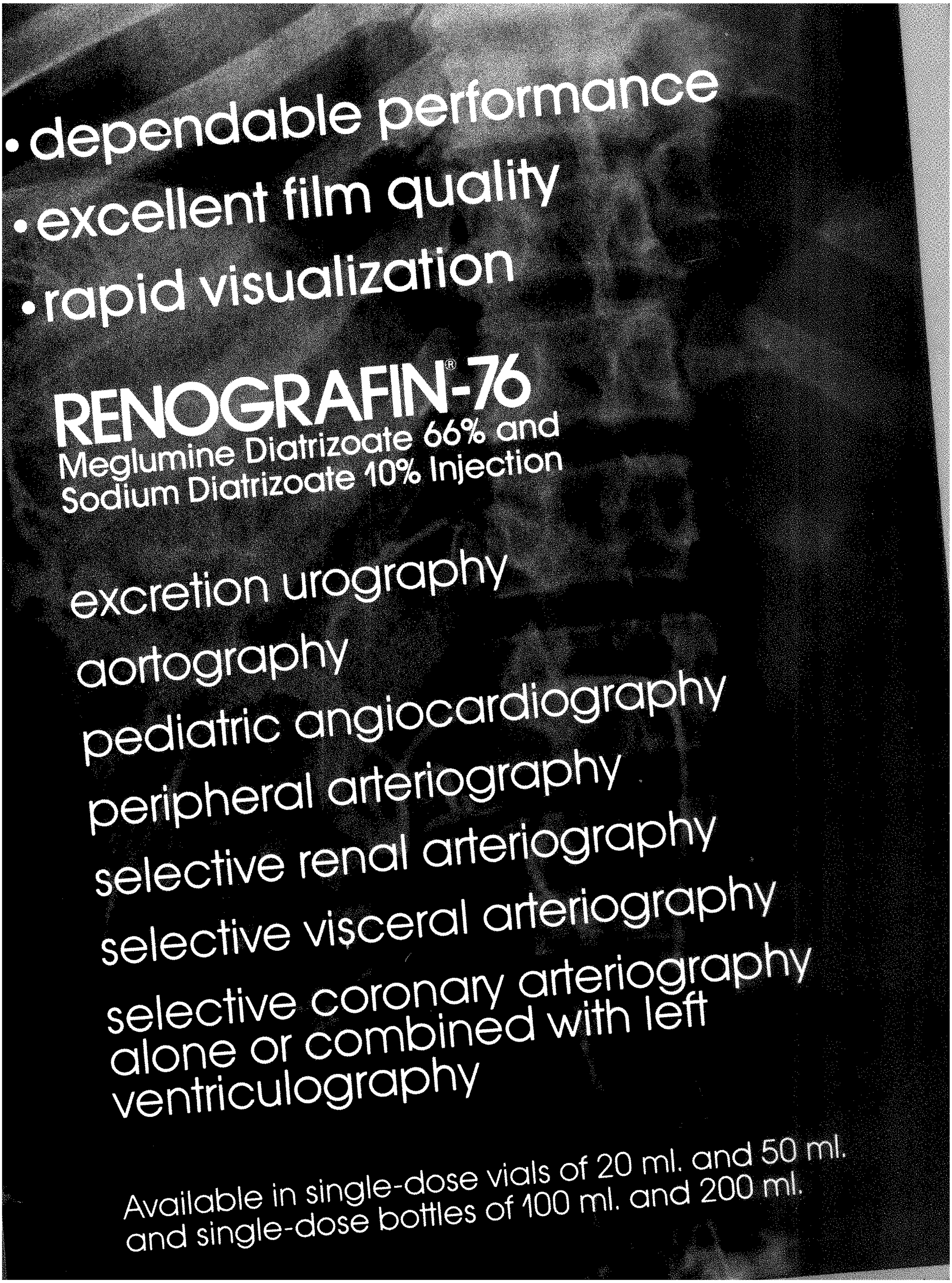
What can you expect from your Kodak Technical Sales Representative? More than the name implies.

Your TSR is a professional consultant — highly trained and technically experienced in imaging technology, with a working background in medical radiography, nuclear imaging, photofluorography, cinefluorography. Here's what the TSR can do:

- Conduct training courses for x-ray department personnel
- Arrange for special courses or group training programs
- Give your staff ready access to comprehensive technical information to help you get the most out of your Kodak films, chemicals, processing equipment
- Provide manuals, product brochures, medical charts, audiovisual presentations, slide lectures, clinical case studies, and a variety of technical publications on radiography

To get the most out of your Kodak products, get the most out of your TSR. Contact your Kodak representative. Or consult your x-ray products dealer. Or write: Eastman Kodak Company, Department 740-B, Rochester, N.Y. 14650.

A commitment to quality



- dependable performance
- excellent film quality
- rapid visualization

RENOGRAFIN®-76
Meglumine Diatrizoate 66% and
Sodium Diatrizoate 10% Injection

excretion urography
aortography
pediatric angiocardiography
peripheral arteriography
selective renal arteriography
selective visceral arteriography
selective coronary arteriography
alone or combined with left
ventriculography

Available in single-dose vials of 20 ml. and 50 ml.
and single-dose bottles of 100 ml. and 200 ml.

RENOGRAFIN®-76

Meglumine Diatrizoate 66% • and Sodium Diatrizoate 10% Injection

Renografin-76 is supplied as a sterile, aqueous solution providing 66% meglumine diatrizoate and 10% sodium diatrizoate with 0.32% sodium citrate as a buffer and 0.04% disodium edetate as a sequestering agent. The solution contains approximately 37% (370 mg./ml.) bound iodine and *approximately 4.48 mg. (0.19 mEq.) sodium per ml.*

CONTRAINDICATIONS: In patients with a hypersensitivity to salts of diatrizoic acid. Urography contraindicated in patients with anuria.

WARNINGS: A definite risk exists with the use of contrast agents in excretion urography in patients with multiple myeloma. There has been anuria with progressive uremia, renal failure and death. This risk of the procedure in these patients is not a contraindication; however, partial dehydration in preparation for study is not recommended since it may predispose for precipitation of myeloma protein in renal tubules. No therapy, including dialysis, has been successful in reversing this effect. Myeloma should be considered in persons over 40 before undertaking urographic procedures.

In cases of known or suspected pheochromocytoma, if the physician feels that the possible benefits outweigh the considered risks, radiopaque materials should be administered with extreme caution; however, an absolute minimum of material should be injected, the blood pressure should be assessed throughout the procedure, and measures for treating a hypertensive crisis should be available.

Contrast media may promote sickling in homozygous individuals when injected I.V. or intra-arterially. Although a history of sensitivity to iodine *per se* or to other contrast media is not an absolute contraindication, administration of diatrizoate requires extreme caution in such cases. Perform thyroid function tests prior to administration of Renografin-76 since iodine-containing contrast agents may alter the test results.

Weigh the inherent risks against necessity for performing *angiocardiography* in cyanotic infants and patients with chronic pulmonary emphysema. In *pediatric angiocardiography*, a dose of 10 to 20 ml. may be particularly hazardous in infants weighing less than 7 kg.; this risk is probably significantly increased if these infants have preexisting right heart "strain," right heart failure, and effectively decreased or obliterated pulmonary vascular beds. Perform *urography* with extreme caution in persons with severe concomitant hepatic and renal disease. Perform *selective coronary arteriography* only in selected patients and those in whom expected benefits outweigh the procedural risk. Perform *selective visceral arteriography* with extreme caution in presence of severe generalized atherosclerosis, specifically with plaques or aneurysms at level of iliac or femoral arteries.

Usage in Pregnancy: Use Renografin-76 in pregnant patients only when the physician deems its use essential to the welfare of the patient since safe use during pregnancy has not been established.

PRECAUTIONS: Diagnostic procedures involving use of contrast agents should be performed under the direction of personnel with prerequisite training and a thorough knowledge of the particular procedure. Appropriate facilities should be available for coping with situations which may arise as a result of the procedure and for emergency treatment of severe reactions to the contrast agent itself; competent personnel and emergency facilities should be available for at least 30 to 60 minutes after I.V. administration since delayed reactions have been known to occur. These severe life-threatening reactions suggest hypersensitivity to the contrast agent. A personal or family history of asthma or allergy or a history of a previous reaction to a contrast agent warrants special attention and may predict more accurately than pretesting the likelihood of a reaction although not the type nor severity of the reaction in the individual. The value of any pretest is questionable. The pretest most performed is the slow I.V. injection of 0.5 to 1.0 ml. of the preparation prior to injection of the full dose; however, the absence of a reaction to the test dose does not preclude the possibility of reaction to the full diagnostic dose. Should the test dose produce an untoward response, the necessity for continuing the examination should be re-evaluated. If deemed essential, examination should proceed with all possible caution. In rare instances, reaction to the test dose may be extremely severe; therefore, close observation and facilities for emergency treatment are indicated.

Renal toxicity has been reported in a few patients with liver dysfunction who were given oral cholecystographic agents followed by urographic agents; therefore, if known or suspected hepatic or biliary disorder exists, administration of Renografin-76 should be postponed following the ingestion of cholecystographic agents. Consider the functional ability of the kidneys before injecting Renografin-76. Use cautiously in severely debilitated patients and in those with marked hypertension. Bear in mind the possibility of thrombosis when using percutaneous techniques. Since contrast agents may interfere with some chemical determinations made on urine specimens, collect urine before or two or more days after administration of the contrast agent.

In *excretion urography*, adequate visualization may be difficult or impossible in uremic patients or others with severely impaired renal function (see Contraindications). In *aortography* repeated intra-aortic injections may be hazardous; this also applies to *pediatric angiocardiography* particularly in infants weighing less than 7 kg. (see Warnings). In *peripheral arteriography*, hypotension or moderate decreases in blood pressure seem to occur frequently with intra-arterial (brachial) injections; this is transient and usually requires no treatment. Monitor blood pressure during the immediate 10 minutes after injection. It is recommended that *selective coronary arteriography* not be performed for about 4 weeks after diagnosis of myocardial infarction; mandatory prerequisites to this procedure are experienced personnel, ECG monitoring apparatus, and adequate facilities for immediate resuscitation and cardioversion.

ADVERSE REACTIONS: Nausea, vomiting, flushing, or a generalized feeling of warmth are the reactions seen most frequently with intravascular injection. Symptoms which may occur are chills, fever, sweating, headache, dizziness, pallor, weakness, severe retching and choking, wheezing, a rise or fall in blood pressure, facial or conjunctival petechiae, urticaria, pruritus, rash, and other eruptions, edema, cramps, tremors, itching, sneezing, lacrimation, etc. Antihistaminic agents may be of benefit; rarely, such reactions may be severe enough to require discontinuation of dosage. There have been a few reports of a burning or stinging sensation or numbness, of venospasm or venous pain, and of partial collapse of the injected vein. Neutropenia or thrombophlebitis may occur. Severe reactions which may require emergency measures (see Precautions) are a possibility and include cardiovascular reaction characterized by peripheral vasodilatation with hypotension and reflex tachycardia, dyspnea, agitation, confusion, and cyanosis progressing to unconsciousness. An allergic-like reaction ranging from rhinitis or angioneurotic edema to laryngeal or bronchial spasm or anaphylactoid shock may occur. Temporary renal shutdown or other nephropathy may occur.

Adverse reactions as a consequence of *excretion urography* include cardiac arrest, ventricular fibrillation, anaphylaxis with severe asthmatic reaction, and flushing due to generalized vasodilatation. Risks of *aortography* procedures include injury to aorta and neighboring organs, pleural puncture, renal damage (including infarction and acute tubular necrosis with oliguria and anuria), accidental selective filling of right renal artery during translumbar procedure in presence of preexistent renal disease, retroperitoneal hemorrhage from translumbar approach, spinal cord injury and pathology associated with syndrome of transverse myelitis, generalized petechiae, and death following hypotension, arrhythmia, and anaphylactoid reactions. In *pediatric angiocardiography*, arrhythmia and death have occurred. During *peripheral arteriography*, hemorrhage from puncture site, thrombosis of the vessel, and brachial plexus palsy (following axillary artery injection) have occurred. During *selective coronary arteriography* and *selective coronary arteriography with left ventriculography*, transient ECG changes (most patients); transient arrhythmias (infrequent); ventricular fibrillation (from manipulation of catheter or administration of medium); hypotension; chest pain; myocardial infarction; transient elevation of creatinine phosphokinase (occurred in about 30% of patients tested); fatalities have been reported; hemorrhage, thrombosis, pseudoaneurysms at puncture site, dislodgment of arteriosclerotic plaques, dissection of coronary vessels, and transient sinus arrest have occurred due to the procedure. Adverse reactions in *selective renal arteriography* include nausea, vomiting, hypotension, hypertension, and post-arteriographic transient elevations in BUN, serum creatinine and glucose. Complications of *selective visceral arteriography* include hematomas, thrombosis, pseudoaneurysms at injection site, dislodgment of arteriosclerotic plaques; other reactions may include urticaria, hypotension, hypertension, and insignificant changes in renal function and liver chemistry tests.

For full prescribing information, consult package insert.

HOW SUPPLIED: Available in 20 ml. and 50 ml. single-dose vials and in 100 ml. and 200 ml. single-dose bottles.

SQUIBB HOSPITAL DIVISION
E.R. Squibb & Sons, Inc.

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SQUIBB®

contrast media™

The Reason is Clear

Name____________________________

No.______________________________

Date____________________________

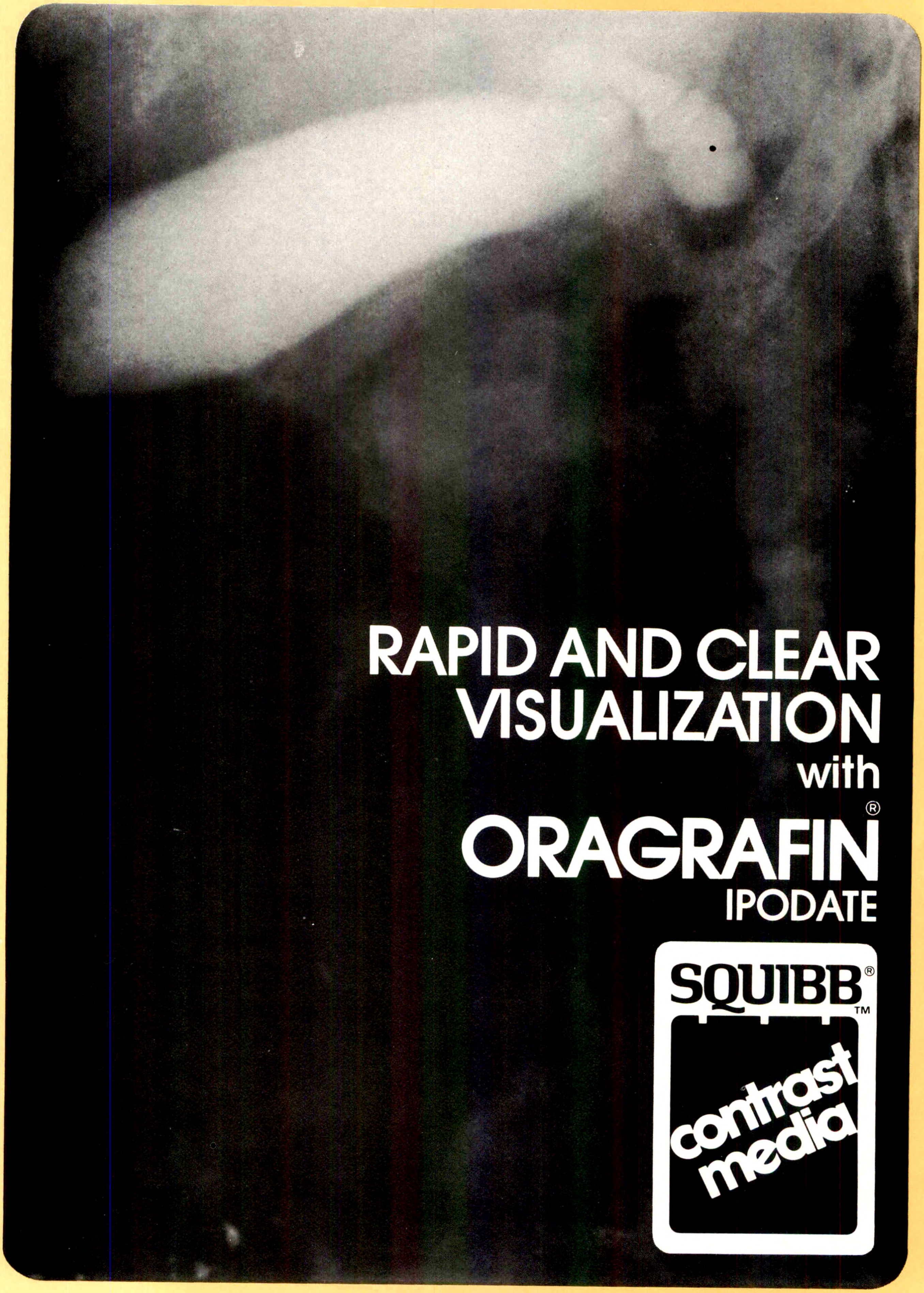
Dr.______________________________

Remarks__________________________

____

____

The
Reason
is
Clear...
Effectiveness


RAPID AND CLEAR VISUALIZATION
with
ORAGRAFIN®
IPODATE
SQUIBB®
contrast media™

- Visualization of the ducts occurs in 1 to 3 hours and of the gallbladder within 5 hours or less with Oragrafin Calcium Granules (Calcium Ipodate for Oral Suspension N.F.).
- The gallbladder is opacified approximately 10 hours after ingestion of Oragrafin Sodium Capsules (Sodium Ipodate Capsules N.F.).
- Rapid absorption often permits visualization of even poorly functioning gallbladders. An unprepared patient can be studied the same day.
- When patients cannot take capsules, the granules are a convenient, palatable alternative.
- Both salts are usually well tolerated.

Dosage Schedules

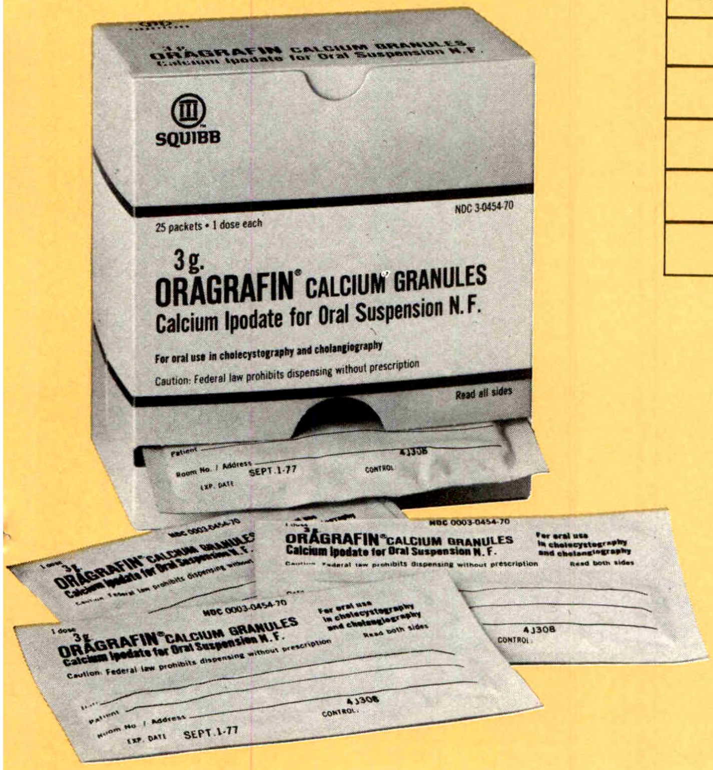
FOR ROUTINE OVERNIGHT PROCEDURES
Sodium Ipodate Capsules and/or Calcium Ipodate for Oral Suspension

	Gallbladder Films		Films of the Gallbladder and Biliary Ducts
11 P.M.	6 Capsules OR (or 12 Capsules)	1 packet of Granules (or 2 packets)	6 Capsules (or 1 packet of Granules, if preferred) and
next morning, 8 A.M.			1 packet of Granules
9 A.M.	Visualization of gallbladder	Visualization of gallbladder	Visualization of ducts and gallbladder
10 A.M.			
11 A.M.			

FOR RAPID, SAME-DAY PROCEDURES
Calcium Ipodate for Oral Suspension

	Films of Gallbladder and Ductal System
8 A.M.	2 packets of Granules
9 A.M.	Visualization of ducts
10 A.M.	Optimal visualization of ducts
1 P.M.	Visualization of gallbladder

See next page for complete prescribing information.


SQUIBB
25 packets • 1 dose each
NDC 3-0454-70
3g.
ORAGRAFIN® CALCIUM GRANULES
Calcium Ipodate for Oral Suspension N.F.
For oral use in cholecystography and cholangiography
Caution: Federal law prohibits dispensing without prescription
Read all sides
SEPT. 1-77
4J308

ORAGRAFIN®
CALCIUM GRANULES
Calcium Ipodate for Oral Suspension N.F.

ORAGRAFIN®
SODIUM CAPSULES
Sodium Ipodate Capsules N.F.

the reason is clear

ORAGRAFIN®
CALCIUM GRANULES
Calcium Ipodate for Oral Suspension N.F.

ORAGRAFIN®
SODIUM CAPSULES
Sodium Ipodate Capsules N.F.

DESCRIPTION
Oragrafin Calcium Granules (Calcium Ipodate for Oral Suspension N.F.) and Oragrafin Sodium Capsules (Sodium Ipodate Capsules N.F.) are oral radiopaque media for cholangiography and cholecystography. *Calcium* ipodate is available in single-dose foil packets providing 3 g. calcium ipodate as granules dispersed in flavored sucrose. When mixed with water, the granules produce a pleasantly-flavored suspension. *Sodium* ipodate is available in capsules providing 500 mg. sodium ipodate per capsule.

The organically bound iodine content of calcium ipodate and sodium ipodate is 61.7% and 61.4%, respectively.

ACTIONS
Calcium ipodate and sodium ipodate are absorbed from the gastrointestinal tract, excreted by the liver into the bile, and stored and concentrated in the gallbladder. The calcium salt, which is absorbed somewhat faster than the sodium salt, appears in the ducts as early as 30 minutes after ingestion. Optimal concentration of either salt in the hepatic and biliary ducts occurs within 1 to 3 hours after ingestion in nearly all cases; rarely, maximal opacification may be delayed for as much as 5 hours. Adequate opacification of the ducts usually persists for about 45 minutes. The ducts may be visualized in patients who have undergone cholecystectomy.

The gallbladder is optimally opacified approximately 10 hours after ingestion of either salt. Diagnostically adequate filling, however, often takes place within 5 hours or less after ingestion, particularly with the calcium salt. Thus, studies of ducts and gallbladder may be carried out in as little as 5 hours when necessary or desirable. In this connection, it should be pointed out that both salts have been administered to unprepared patients as well as to previously prepared patients, with no significant difference in results.

INDICATIONS
Calcium ipodate and sodium ipodate are indicated for cholecystography. They may also be used for cholangiography, although they are not considered the drugs of choice.

CONTRAINDICATIONS
Both preparations are contraindicated in persons who are hypersensitive to ipodate salts.

WARNINGS
A history of sensitivity to iodine *per se* or to other iodinated compounds is not an absolute contraindication to the use of these preparations, but calls for extreme caution in administration.

Usage in Pregnancy
The safety of these preparations for use during pregnancy has not been established; therefore, they should be used in pregnant patients only when, in the judgment of the physician, their use is deemed essential to the welfare of the patient.

PRECAUTIONS
Increasing the dosage above that recommended increases the possibility of hypotension.

Anuria may result when these preparations are administered to patients with combined renal and hepatic disease or severe renal impairment.

Renal toxicity has been reported in a few patients with liver dysfunction who were given oral cholecystographic agents followed by urographic agents. Administration of urographic agents should therefore be postponed in any patient with a known or suspected hepatic or biliary disorder who has recently taken a cholecystographic contrast agent.

Gastrointestinal disorders which interfere with absorption and liver disorders which interfere with excretion may result in non-visualization of the hepatic and biliary ducts and the gallbladder.

Contrast agents may interfere with some chemical determinations made on urine specimens; therefore, urine should be collected before administration of the contrast media or two or more days afterwards.

Thyroid function tests, if indicated, should be performed prior to the administration of these preparations since iodine containing contrast agents may alter the results of these tests.

ADVERSE REACTIONS
Sodium ipodate and calcium ipodate are usually well tolerated. Unwanted effects such as mild and transient nausea, vomiting, or diarrhea sometimes occur but the incidence can be reduced by restricting the dosage to 3 g. and administering only the Granules to patients who may be prone to gastrointestinal reactions. Headache, dysuria, or abdominal pains may occur infrequently as transient disturbances.

Hypersensitivity reactions may include urticaria, serum sickness-like reactions (fever, rash, arthralgia), other skin rashes, and, rarely, anaphylactoid shock. They are more likely to occur in individuals with a history of allergy, asthma, hay fever, or urticaria, and in those who have previously demonstrated hypersensitivity to iodine compounds.

DOSAGE AND ADMINISTRATION
The Capsules should be taken with as little water as possible. They may be swallowed in rapid succession or slowly over the course of ½ hour or more, depending on patient preference.

The Granules should be stirred vigorously into a small amount of water (¼ glass or less) and swallowed immediately. If lukewarm rather than cold water is used, the patient will find the suspension quite palatable and there will be less likelihood of nausea.

A total dose of 6 g. (12 Capsules or 2 packets of Granules) per 24 hour period should not be exceeded.

When an upper gastrointestinal barium study is scheduled, prior administration of either salt will not interfere. Either salt may also be used in conjunction with an intravenous cholangiographic agent.

The recommended dosage and patient preparation for cholangiography and/or cholecystography are as follows:

Routine Cholecystography
On the day before the examination, the patient may, if feasible, eat a high-fat lunch so that the gallbladder will evacuate and refill with opacified bile. The evening meal, which should be light and fat-free, should be eaten 2 hours before the contrast medium is taken. The contrast agent should be administered 10 to 12 hours before the roentgenologic examination. The usual dose is 6 Capsules (providing 3 g. sodium ipodate), although up to 12 Capsules may be given; 1 to 2 packets of Granules may be used instead. No other food or drink except small amounts of water should be taken before the examination. A mild laxative or other cathartic may be given, but is not generally necessary.

Roentgenologic examination of the gallbladder is performed the next morning in the usual manner, employing the standard positions. An immediate study of the wet films will determine any need for repositioning of the patient. Administration of a fat meal or other cholecystokinetic agent provides good dynamic studies of gallbladder function. If a barium meal examination is also to be performed, the fat meal may be given simultaneously with or following the barium meal. Gallbladder function studies are then made after the barium meal examination is completed.

Cholangiography
No prior preparation of the patient is necessary. For this procedure, the Granules should be used. They are administered one hour before cholangiography. Although only one packet (providing 3 g. calcium ipodate) may suffice, two packets (6 g.) are usually necessary for visualization of the ducts.

Beginning one hour after ingestion of the Granules, and at 15-minute intervals thereafter, films should be taken, preferably with the aid of tomography or laminography. With proper positioning of the patient, residual contrast medium in the gastrointestinal tract is not likely to be a problem, particularly with the more rapidly absorbed calcium salt. Optimal visualization of the ducts is generally achieved between 1½ and 2½ hours after ingestion of the medium.

Combined Cholangiography and Cholecystography
Preparation of the patient and administration of dosage should be as outlined under *Routine Cholecystography*, with a dosage of 6 Capsules or, if preferred, one packet of Granules taken on the evening before examination. On the following morning, one hour before the examination, one additional packet of Granules should be administered.

Beginning one hour after the morning dose, and at 15-minute intervals thereafter, films should be made, preferably with the use of tomography or laminography. While the gallbladder will have concentrated the evening dose of the medium, the additional morning dose will provide opacification of the ducts, and simultaneous visualization may be achieved. When satisfactory films have been obtained, a fat meal may be administered to provide gallbladder function studies.

Rapid Combined Cholangiography and Cholecystography
No prior preparation of the patient is necessary. On the day of examination, the patient should be given two packets of Granules. Beginning one hour later, examination of the ducts should be performed as described under *Cholangiography*. If the gallbladder has not opacified sufficiently by the time the cholangiographic examination is completed, further cholecystograms may be taken after 2 or 3 hours. Dynamic studies of gallbladder function may be carried out in the usual manner.

HOW SUPPLIED
Oragrafin Calcium Granules (Calcium Ipodate for Oral Suspension N.F.), single-dose foil packets; boxes of 25 packets (3 g. calcium ipodate per packet). Oragrafin Sodium Capsules (Sodium Ipodate Capsules N.F.), boxes of 25 vials (6 capsules each vial); bottles of 100; and Unimatic® single-dose packages of 100.

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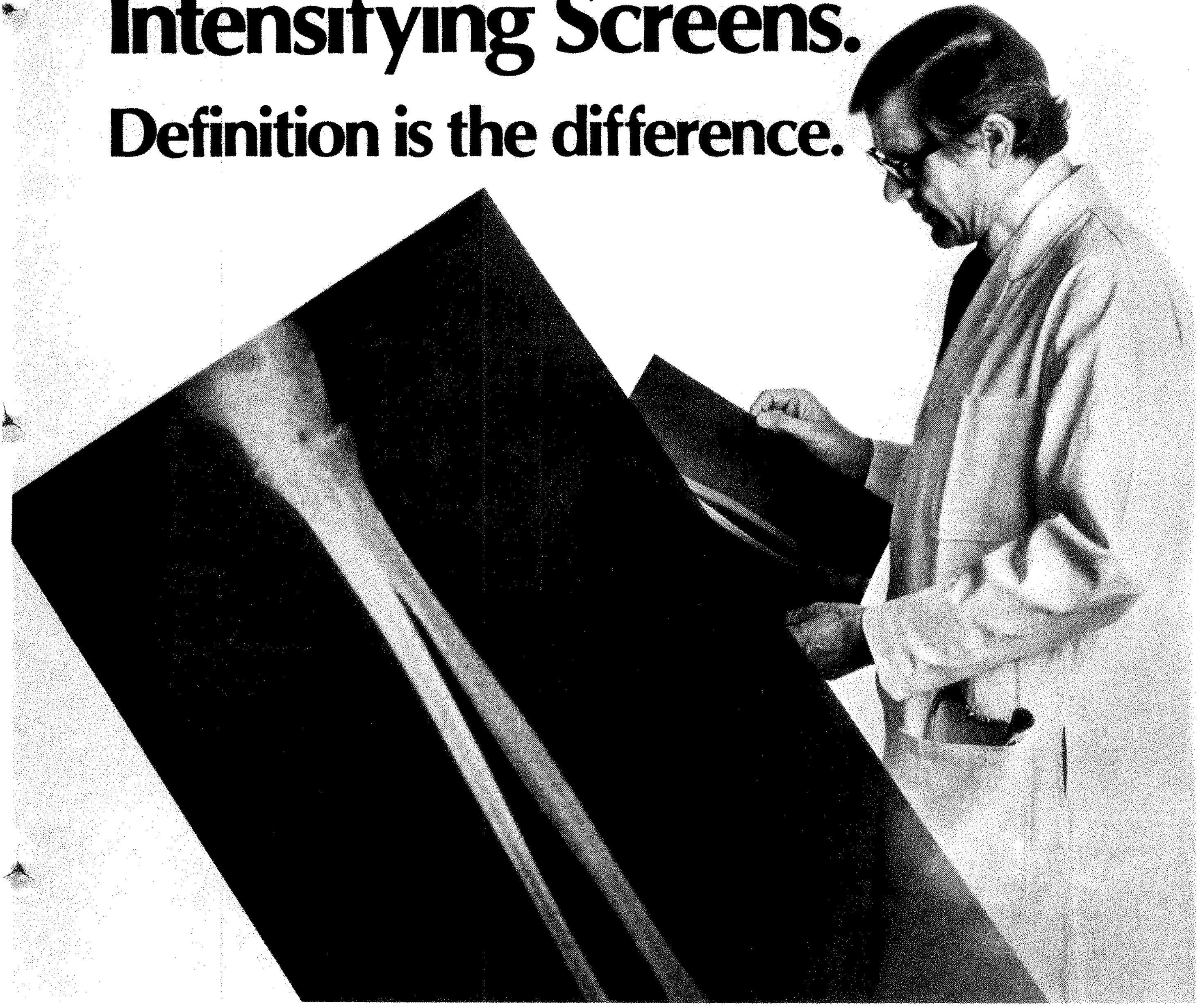

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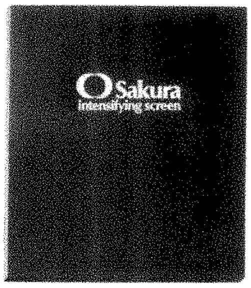

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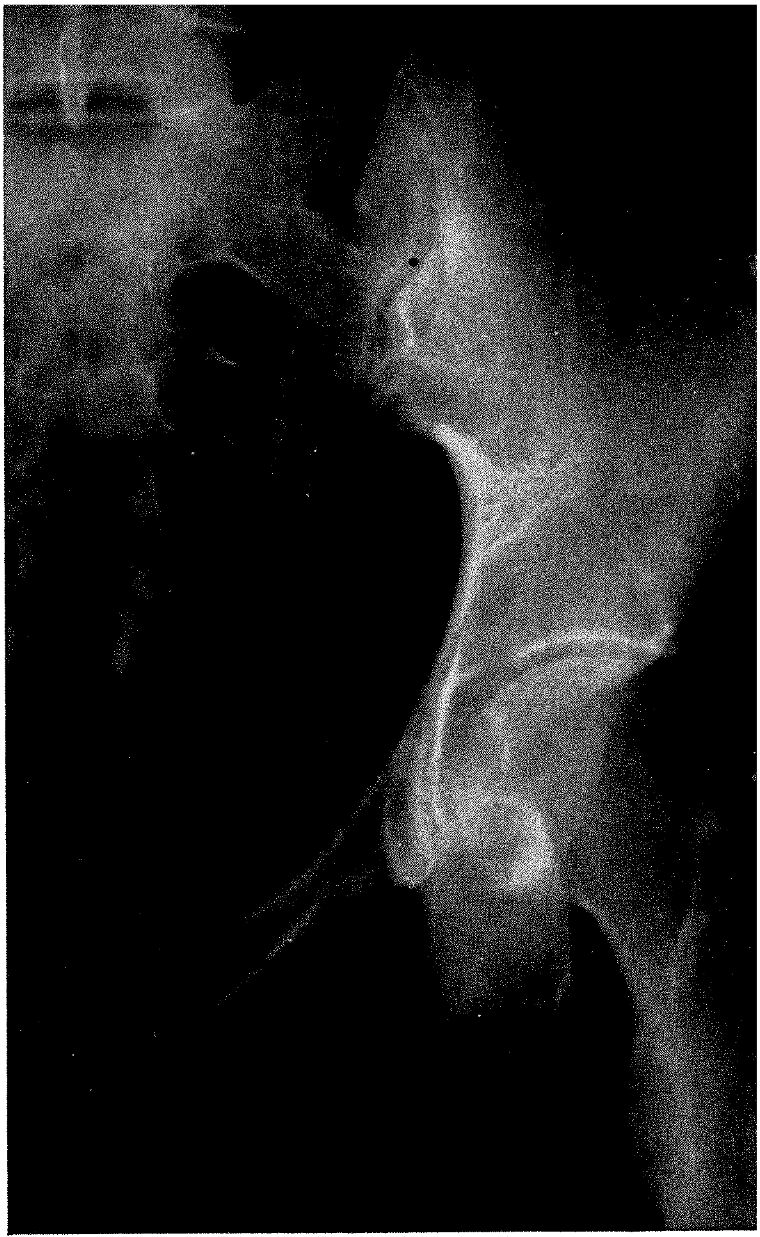

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OVARIAN CANCER: MULTIFACET DISEASE; MULTIFARIOUS THERAPY AND THERAPISTS*

JANEWAY LECTURE, 1975

By GEORGE C. LEWIS, JR., M.D.†
PHILADELPHIA, PENNSYLVANIA

WHILE the title of the 1975 Janeway Lecture suggests a limited topic, the presentation has structured into it the concept that ovarian cancer shares many of its characteristics with other malignancies. We still have a lot to learn about these characteristics, especially as they relate to clinical management of cancer. In this sense the parameters or characteristics of malignancy act as a form of roadblock to cancer control. By increased understanding of each aspect of cancer as treatment programs are developed and evaluated we should be able to put aside the obstacles and either prevent or eradicate malignant disease.

The parameters of ovarian cancer when scrutinized in detail can appear as a kaleidoscopic view, blending one picture almost imperceptibly into another as we turn from one histologic type to another and from one patient population to another. The incidence of various characteristics changes so from patient to patient that the clinician may not appreciate it when he looks at his patients using rather gross consideration by stage or histologic type. As a result there is a tendency to overlook some of the more subtle influences that may significantly change the final tint or tone of the clinical picture. This natural tendency to a gross overview may be causing us to miss some more obscure and limited responses of neoplasia to our treatment, these nuances being lost in the blurred picture of our over-all results which continue to be static and certainly discouraging. This in turn leads to literal literary handwringing because we appear unable to change the prognosis for this and similar malignancies.

The generally discouraging picture for ovarian cancers may be perpetuated, at least in part, by our failure as clinicians to be willing to focus down on the multitude of interrelationships that seem to correlate with survival. Webb and his collaborators,[19] in commenting upon some of the clinical correlations, noted that there must be confusion for the clinician when it comes to choosing the most appropriate treatment for his patient who has some one of the many variations of ovarian cancer. Webb indicated that a more organized approach to clinical research, at least in ovarian cancer, might be helpful in establishing some guidelines to treatment. It is possible

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* Presented at the Fifty-seventh Annual Meeting of the American Radium Society, Isla Verde, Puerto Rico, May 4–9, 1975.

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Table I

BASIC THEMES OF REPORTS RELATED TO OVARIAN CANCER

1. Lethal = 70 percent die
2. Leading gynecologic cancer mortality
3. Patients in Stage III or IV = 70 percent
4. Epithelial malignancy = 70 percent
5. Surgery can spell success or failure
6. Exact comparable series lacking
7. Need for multi-institutional cooperation

that a better understanding of the tumor's parameters might improve the results of therapy without the aid of significant refinement of treatment techniques or programs.

During my childhood the fates afforded me the dubious advantage of three surgical procedures under nitrous oxide and ether. My memory serves me too well in recalling the mental picture encountered with each induction. There was a great black space with three or four fiery doughnuts floating and drifting about. I ran around desperately trying to catch one, then another, and trying to put one inside another endlessly feeling all the while terribly frustrated.

This tale is told not to give Freudian vindication for my choice of gynecology over surgery or radiation therapy as a career. Rather the induction fantasy seems to me to parallel the present state of the art in the management of ovarian cancer. The constantly varying pictures of ovarian cancer populations in each of our institutions enigmatically beckon to us to be grasped and resolved. It is the failure to do so after so many tries that proves so frustrating.

In the reports that deal with ovarian cancer there are oft repeated themes[2,5–7,15,18,19] (Table I). Collectively considered the malignancies are highly lethal. Their lethality exceeds that of other gynecologic malignancy. Diagnosis is first established for 65 percent to 70 percent of patients as Stages III or IV. The bulk of malignancies are in the epithelial category. Cure is largely due to the fact that a surgical specialist happened to cut out all the malignancy the body is incapable of handling. Exactly comparable series of patients are lacking in published reports of treatment. In fact many of the initial detailed data about the disease, the patients and the results, are missing or mixed into the general conglomeration of information peculiar to the reporting institution. It is hard to contrast sensibly different reports because of lack of uniformity in grouping patients by disease and treatment subcategories. One recent article[10] on drug therapy for ovarian cancer is of interest because of the extreme it represents in that in the course of contrasting two different chemotherapeutic regimens, there is no mention of any tumor characteristics except advanced Stage III and IV ovarian cancer without prior irradiation or chemotherapy. Finally some authors recognize the points mentioned and agree that ovarian cancer must be dealt with on a collaborative multi-institutional basis to collect large enough groups of patients.

The many suggestions as to what can or cannot be done for ovarian cancer and the many commentaries about various aspects of ovarian cancer are somewhat akin to Mark Twain's views as to the weather. I must hasten to add there is a difference; some individuals are trying to do something about it, although perhaps not all in the same direction; limited progress is occurring.

Despite the fact that we talk about ovarian cancer as a sort of single entity it is not just a disease but a multifacet conglomerate of tumors. There is a minimum of 15 histologic types[11,16] (Fig. 1). The histologic concept of cancer is muddied by the necessity to include in our consideration the borderline or questionable malignancies. Such tumors may be microscopically rather innocent but clinically exhibit gross characteristics of many malignant neoplasms. If we include these variations there are potentially 24 histologic varieties. Add differentiation of four grades[7] and one can be dealing with 61 varieties of tumor patterns. Simple staging I to IV expands our varieties to 241, providing that we drop the borderline non-epithelial tumors. Substaging* to IA, IB, IC, etc.,[16] expands our combination to 424. ¶If we add just one more variable picked at random from the many we could choose, for example tumors residual after surgery and greater or less than a specified size[8,15] we could achieve 604 varieties, quite a few more than Heinz started with. It is obvious that the statistical computation of variables results in a much larger number than illustrated. This discrepancy is explained by the elimination of non-existent situations. As an example, solid, undifferentiated, epithelial malignancies were not separated into four grades.

It could be rightly argued that the great number of varieties cited does include quite a number of very rare non-epithelial tumors. In addition most articles in the literature tend to be limited to the topic of epithelial tumors. If the same analysis were repeated using only these tumors and if we were to drop the possibly malignant tumors (Fig. 2) there would be four histologic types, ten variations with three grades of differentiation, 40 varieties with staging, 70 with substaging and a mere 100 varieties with division by more or less than a specified size of residual tumor. Thus it is possible under the conditions specified to have in a group of 100 women with ovarian cancer no two patients exactly alike, from the neoplastic viewpoint.

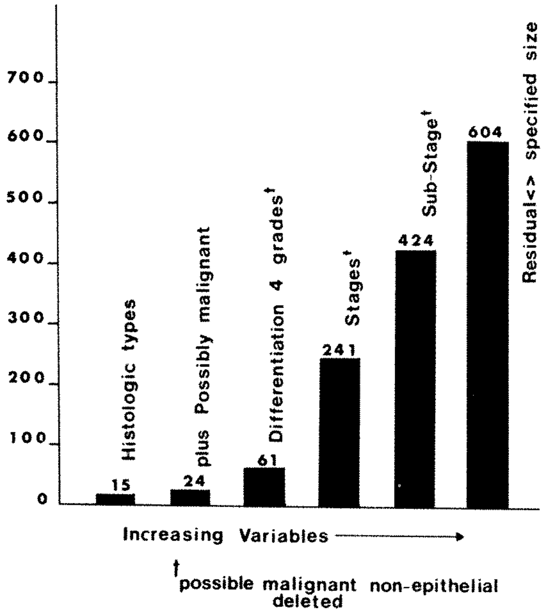

FIG. 1. "Cumulative" effect of multiple variables representing tumor related parameters for population with ovarian cancer.

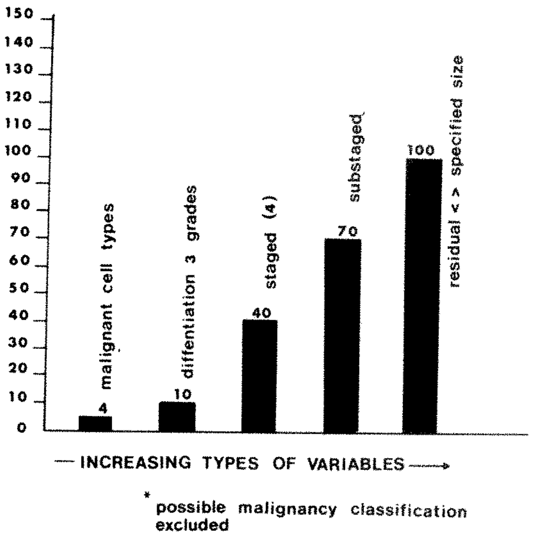

FIG. 2. "Cumulative" effect of multiple variables representing tumor related parameters for patient population with epithelial ovarian cancer.*

* Pre-1975 F.I.G.O. Staging System.

The all too frequent escape from this great potpourri is to ignore the fine details and to refer to patient populations in rather broad categories, as previously noted, of stage and cell type ignoring substage differentiation, size of residual tumor, and many other factors. Cell type is analyzed relative to results separately from stage and *vice versa.* A multifactoral analysis tying together a number of aspects is just not customary. It really is impossible because for a given institution there are not enough cases to make the more unusual categorical combinations worth studying.

Some of the facets of the ovarian malignancies appear to have more relation to the results of treatment than the treatment itself. Thus different incidences of these factors within different populations of patients may have to do more with the results than the different ways in which they happened

TABLE II

EFFECT OF PATIENT DISTRIBUTION ON APPARENT SURVIVAL
ALL PATIENTS ASSUMED TO BE STAGE I OVARIAN CANCER

Institution A				Institution B		
No. at Risk	No. Survivors	Survivor Rate (percent)		No. at Risk	No. Survivors	Survivor Rate (percent)
10	8	80	"M"	90	72	80
90	27	30	"S"	10	3	30
100	35	35		100	75	75
10	8	80	"M"	90	54	60
90	27	30	"S"	10	1	10
100	35	35		100	55	55

"M", "S" = histologic types.

to be treated. Obviously it is also possible for two groups treated in an exactly identical manner to have entirely different survivals. The relative incidence of favorable and unfavorable factors may produce some odd effects upon results. In Table II for instance there can be shown the effect of numbers and differences in survival for two cell types. Two institutions, A and B, may have identical survivals for each of two different cell types "M" and "S" but if institution A has more of the "S" type tumors and B has more of the "M" type the over-all result for each group will appear better at B than at A. It is also possible that inferior results, say, at institution B for each cell type might be concealed by the fact that B had many more patients, relatively speaking, in "M" than in "S." Looking at the over-all results would lead to the natural conclusion that treatment was better at B than at A. Tumor related parameters do lead to different results as shown by a few selected examples in Figure 3. Serous and mucinous tumors exhibit differences in survival.[7] Stages produce differences. We usually don't think of correlations with grade.[7] The relation of survival to possible *versus* actual malignancy is recognized.[14,16] Of interest is another observation relative to the presence of psammoma bodies.[3] As noted in Figure 3 survival can vary from 48 to 89 percent in Stage I and from ten to 80 percent in Stage II. As stage groupings are broken up into smaller categories the number of patients for comparison gets pretty slim even for large volumes of patients in single institutions as noted in the excellent reports of Decker *et al.*[7] and Webb *et al.*[19] In grading patients in Stages I and II in Decker's report the patients were separated into eleven groups containing from two to 84 patients. Aure and associates,[3] in discussing the same stages, serous cystadenocarcinoma, and the presence of psammoma bodies, had four groups with patients varying in number from six to 50. If one were to subdivide staging for both reports and if for Aure's report one were to add grading, the result would be to have a lot of categories with few to no patients within each subdivision.

A comparison of relatively general categories like stages still has the problem of attaining significance from a purely statistical viewpoint even if we ignore the possible impact of variations of parameters under the broad classes. If we make a hypothetical comparison of Decker's[7] results for serous carcinoma Stage I with 88 survivors

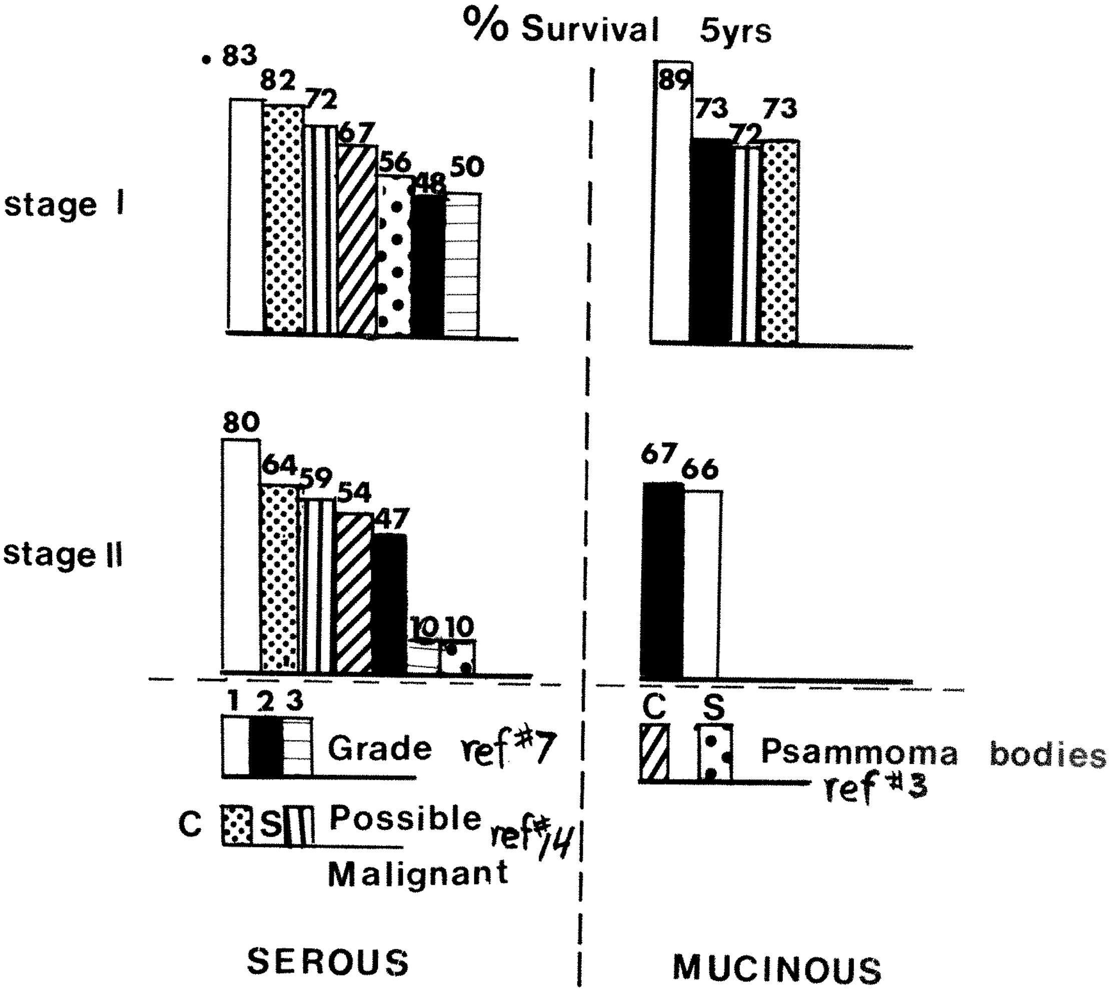

Fig. 3. Apparent effect in survival from specified variables representing tumor related parameters.

in 134 patients (Table III) with those reported by Nieminen and Purola[14] for the same stage and cell type with 41 survivors among 57 treated patients, there is no significance to the six percent difference. To my knowledge neither of these investigators has reported a contrast of their results nor made any claims relative to each other as they were selected for this presentation as random samples. However, if they were to make such a contrast assuming the same percentages of survival for each author

Table III

OVARIAN CANCER SURVIVAL FOR STAGE I SEROUS CYSTADENOCARCINOMA

Report	Survivors	Dead	Total	Percent Survival
Decker *et al.*[7]	88	46	134	66
Nieminen and Purola[14]	41	16	57	72
Minimum required per group for significance			500	

they would have to achieve their results with about 500 comparable patients each to attain a six percent difference that was significant. Not many places are going to have that number of Stage I patients available within a reasonable period of time.

As suggested by Webb *et al.*[19] extracystic growth, adhesions, and ruptured cysts as encountered in Stage I lesions constitute adverse findings. He suggested recognition of such factors in performing studies and arranging contrasts between more homogeneous groups of patients in order to try to arrive at meaningful results. Certainly these factors like others already cited may vary from group to group, further confusing the physician in his interpretation of the value of his treatment. While ovarian cancer staging modifications recently adopted by F.I.G.O. take cognizance of these and other factors, the change-over in staging also may produce more confusion for the operating surgeon and others.

Obviously, ovarian cancer will not alalways be the patient's only illness. Treatment results of nearly all malignancies take into accounting in their reporting the item "died: intercurrent disease." There are in addition more subtle effects of nonmalignant conditions that are not so readily counted. I refer to surgery not performed because of medical restrictions and to the hepatic, renal, pulmonary, cardiac, and hematopoietic problems that affect chemotherapeutic decisions.

In this year of expanding publicity about the American Bicentennial and the attention given to Paul Revere and his mount, I hesitate to note that the therapist and therapy are as interrelated as horse and rider as both set out to deal with an invading force. Several years ago, Dr. Antolin Raventos and I[17] looked through the retrospectroscope to look at this combination of horse and rider—therapy and therapist. We noted in a review covering many years at the Hospital of the University of Pennsylvania that it was impossible to assign to any one method of therapy any definite credit for the success or failure that occurred in the different categories studied because it appeared that the picture was dominated by the therapist—his indefinable biases, emotions, and intuitions. These were all not definable, especially when one went back over many years, and physicians varied over the years in their attitude. No conclusions could be drawn because of the greatest enigma of them all—the therapist.

In the broadest sense this person who treats ovarian cancer is not one type of individual nor one type of specialist. He is family doctor, general surgeon, urologist, proctologist, hematologist, medical oncologist, obstetrician-gynecologist, radiation therapist, or gynecologic oncologist. To quote from "The King and I": "etc., etc., etc." The first encounter with a specific malignancy may involve any one of these varieties. The subsequent path may be profoundly affected by this person's knowledge, skill and bias. Unlike the situation for cancer of the cervix and of the endometrium, surgery for ovarian cancer almost always precedes established pathologic diagnosis and staging. It means more precisely that the first entry onto the scene and first critical decision, possibly affecting life and death is more likely to be made in ovarian cancer than in the others by individuals with less experience and judgement to set up subsequent programs of management. Many of the initial therapists will unfortunately be individuals who will have nothing further to do with the patient—not even follow-up. As a result the feedback system so essential to self assessment and ultimately to future success will be missing.

Surgical management is basic to therapy and diagnosis. There is general agreement that hysterectomy and bilateral salpingo-oophorectomy are to be performed when the patient appears to be a satisfactory surgical risk and the resection will not apparently compromise survival. Adequate resection to achieve tumor eradication is pretty much confined to Stage I and Stage

IIA patients. On occasion a less skilled surgeon may perform inadequate surgery. In this case there should be no hesitation in re-exploring and carrying out adequate resections. Relatively radical surgery certainly may be performed at times to extirpate segments of bowel, bladder, and ureter, but there is no adequate experience to extablish that this will prolong life. Certainly on some special occasions a degree of worthwhile palliation and a very rare "cure" may be achieved.

After surgery the course depends tremendously upon the guidance of the surgeon. If he has relatively limited experience he may have for security relatively fixed patterns of management requiring not too much of a decision process. Routines of referral develop and individualization may become very minimal. What may have been most effective treatment in properly qualified hands and facilities may become almost unrecognizable in transition from more complex but more effective drug and irradiation programs to protocols of expediency molded to fit geography, limited personnel, limited equipment, limited knowledge, etc. Expediency may unfortunately be favored over critical appraisal of treatment by randomized prospective study. The potential for variation in therapy is infinite. There can be shadings of everything—time, dose, extent, frequency, sequence, intervals, fractionation, loading, maintenance, route, etc. This boullabaisse of therapy, therapists and parameters of disease accounts to a great extent for the confused picture of ovarian cancer management today. Irradiation has been called everything from good to bad.[4,8,12,14,15,18,19] Drugs have been noted as rarely curing any malignancy;[4,9,13] surgery alone has been claimed as curative[1,14] or as being acceptable only with some form of adjuvant therapy.[12] Without controlled studies this great changing mixture of factors can assist researchers in arriving at almost any conclusion: that intracavitary radioactive isotopes are more effective than external strip irradiation, that chemotherapy is more effective than irradiation, and that any one of a number of agents or combination thereof is better than any other.

About 15 years ago several gynecologists and radiation therapists in Philadelphia collaborated in a study that contrasted nitrogen mustard against table salt as an adjuvant to "standard" therapy: surgery plus adjuvant in Stage I; and surgery, irradiation, and adjuvant for Stage III. All 20 of the Stage I patients in the study and three of 75 Stage III patients survived free of disease at least five years. Two of the three Stage III survivors received nitrogen mustard. The conclusion could be (tongue in cheek) that salt is as effective as nitrogen mustard in the control of ovarian cancer. More obviously the patient populations had more influence upon the results than the chemotherapy. It is possible that in a similar manner other studies have come to the point of demonstrating pseudoeffectiveness for some modality or procedure when indeed a disease, patient or therapist factor, unrecognized, played a more critical role in the outcome.

One of the basic arguments that has been running for years is as to the value of adjuvant irradiation, especially for Stage I disease. Artner and Beck,[1] for example, claimed that irradiation was a factor in reduced survival for Stages IA and IB (Table IV). They reported two survivals of four patients treated by surgery alone but only six survivals out of 15 patients treated by the combination of irradiation and surgery. Their conclusion pointed to the superiority of the 50 percent surgery survival over the 40 percent combination survival. It would take a 30 percent difference in survival for comparable groups each of 20 patients to suggest significance, not a ten percent difference for four *versus* 15 patients. Nieminen and Purola[14] in a similar contrast, but including all Stage I lesions, argued the value of surgery alone by pointing to a 93 percent survival for 30 patients. They noted that the addition of irradiation for 80 patients

Table IV

EXAMPLES OF CLAIMED SURGICAL SUPERIORITY FOR OVARIAN CARCINOMA

	Surgery Alone	Surgery plus Irradiation
From Artner and Beck[1]		
Stages IA, IB		
Survivors/total No.	2/4	6/15
Percent survivors	50	40
From Nieminen and Purola[14]		
Stage I		
Survivors/total No.	28/30	59/80
Percent survivors	93	74

resulted in a 74 percent survival. However, they did admit that the surgery only group had an indeterminate number of borderline malignancy patients, a category apparently not to be found in the irradiated patients.

Medically speaking, "ovarian cancer" seems to respond to almost everything to some degree,[11] to alkylating agents, antimetabolites, alkaloids, antibiotics, and possibly to some forms of immunotherapy. Carter[5] (Table V) in a recent review noted a range of responsiveness for most agents from about 30 to 50 percent. The problem still to be faced is the matching of these agents with the many variants already cited.

In Stage I disease the addition of drugs or of irradiation or of combinations may do little to change the prognosis from that achieved for surgery alone. Beyond this, things are very much unknown: what is best for rupture of a cyst? What to use for growth on the peritoneal surface? Are some approaches better for less differentiated tumors than for others?

In Stages III and IV and possibly Stage IIB, and in the newer subdivisions chosen by F.I.G.O., the results are so discouraging that it appears best to concentrate efforts not on survival but upon response and duration of response. Quality of life should outweigh consideration of numerical values of years and survivors. As patterns of response are worked out and as more homogeneous groups of patients are studied there may be some indications of the best means for the useful extension of worthwhile life.

Just prior to the start of the 70's a number of investigators representing different disciplines of medicine approached the National Cancer Institute of the N.I.H. with a number of proposals as to the pursuit of research in gynecologic oncology. Dr. Lawrence Foye at the N.C.I., noting the advantages already gained from other cooperative groups up to that point in history, encouraged the formation of the Gynecologic Oncology Group. It was felt that this would be an excellent means for focusing everyone's efforts in fields of research such as noted in this discussion. The group has now expanded to 34 cooperating institutions. It has currently 19 protocols with several in the process of adoption. The yearly enrollment after three and one-half years of funding and patient entry now exceeds 1,500 patients. The collective registry load of all the institutions involved is shown in Table VI. Of the 9,836 patients with pelvic malignancies admitted to the hospitals, 812 with ovarian cancers were entered into G.O.G. protocols. In 1974, (Table VII) the 2,283 patients included 288 patients with ovarian malignancy. The stage distribution for the previously untreated patient is given in Table VIII. The percentage of entry of patients into protocols needs to be and is being increased to

Table V

OVARIAN CANCER RESPONSE TO CHEMOTHERAPEUTIC AGENTS

Drug	No. Evaluable	Percent Response
Melphalan	366	47
Cytoxan	262	44
Chlorambucil	390	51
Nitrogen mustard	8	50
5 FU	101	32
5 FUDR	35	34
Vinblastine	20	15
Hexamethylmelamine	22	36

take advantage of as many of the available patients as possible. For multi-armed studies there will need to be variations in the size of patient groups from 20 or 30 up to 500 or more each. It is obvious that large numbers of patients will be needed. Greater use of material from registries, while helpful, will not be adequate to fulfill our needs. Recruitment of additional institutions will be essential if we are to have a reasonable patient base.

At this point it would appear appropriate to conclude that the Gynecologic Oncology Group will, through its effect of "togetherness," accomplish much of what needs to be done. Unfortunately things are not quite so simple. Against this concept that the Gynecologic Oncology Group is off and running is the development of apparent splintering in the patient population now being so diligently sought. This could well mark a return to the state of affairs that existed prior to the appearance on the scene of multi-institutional interdisciplinary cooperative groups. Diversification of research paths along which patients may be taken seems to this observer to be developing without over-all direction or coordination that might compensate for the splintering. The potential pathways along which patients may be siphoned off to isolated investigational pools are: the cooperative groups under the Clinical Investigations Branch, the Division of Cancer Treatment, individual Cancer Centers under the Cancer Center Program, the developing programs under Cancer Control and Rehabilitation, and Task Force programs. This listing does not consider contracts nor grants to specific institutions or individuals. To complicate things further several of the cooperative groups have broadened their areas of interest to the point that the degree of overlap is becoming quite significant. However, in May 1975 a cooperative group conference may resolve some of the last problems. If diversification continues, patients with ovarian cancer may be parcelled out in at least four different directions to various competing unrelated investigators. Research into breast cancer and other malignancies appears to be following the same pattern. The over-all situation creates the impression that the programs of governmental groups, divisions, and branches are being pitted against each other. The original picture was that of diverse programs for investigation with some degree of coordination. Group formation has brought together numerous institutions into cooperative efforts; now we seem to be shifting back to what looks for all the world like the original multiscatter pattern. The clinical fields of investigation need to be organized in a serial multi-phase type of arrangement patterned after the tight organization of early steps in

Table VI

GYNECOLOGIC ONCOLOGY GROUP

Registry Entries Reported by Participating Institutions—Pelvic Malignancy May 1, 1971–Dec. 12, 1974

No. of Institutions	Total Registry Load	Registry 1974 Only	Registry Last 6 Months
31	9,836*	2,283	1,714

* Of this number 812 patients with ovarian cancer were entered into G.O.G. Protocols.

Table VII

GYNECOLOGIC ONCOLOGY GROUP

Registry Experience 1974 by Site of Origin

Vulva	Vagina	Cervix	Uterus	Ovary
119	68	1,266	542	288

Table VIII

GYNECOLOGIC ONCOLOGY GROUP

Registry Experience 1974 Stage Distribution for Staged Lesions—Ovarian Cancer

	Stage I	II	III	IV
No.	39	36	105	40
Percent	17.7	16.4	47.5	18.2

laboratory and human clinical trials of drugs. Organizations that have relatively few highly coordinated gynecologists and a reasonably large number of patients with pelvic cancer can play specialized roles such as specific drug screening for initial indications of relative value. Linked together with these could be cooperative groups with huge numbers of patients. Their physician population does not need to be a liability but rather an asset. As they illustrate that a protocol functions for so diverse a group so will it work in actual practice across the country where management of patients may more match a group situation than a single institution's. In single institutions there may be frequent peculiarities inherent to location function or development. While these situations can provide a more controlled environment for research, they cannot produce the patient population nor the broad spectrum of conditions that characterize the situation throughout the country.

In the discussion of their report on the value of grading ovarian cancers, Decker *et al.*[7] noted the need for cooperative studies. They admitted that single institutions did not have the material to provide the required answers. They also commented upon the deficits of cooperative groups. It would seem that we need a bit of both. Protocols developed in one place may not fit all others no matter how excellent the originating institution. It would seem that the excellent institution could develop the programs as pilot studies and the cooperative group could field test and modify them to make them more universally applicable. Certainly not all the patients in the United States will be handled in one or two excellent institutions, but through program development excellence can be carried to the networks of cancer management throughout the country. We are thus at a point in the development of cancer research when some decisions are to be made. The decisions must set up objectives which will utilize as much as possible all the resources available on a more organized basis than is currently apparent.

It has to be concluded that the future holds several possibilities for us as researchers in clinical management of cancer:

1. We can regress by proliferating programs that are competitive and not appreciably coordinated, resembling nomads in a desert never going nor getting anywhere, or at best achieving objectives after long delay; or
2. We can hold where we are administratively and hope that the various objectives set by the programs everywhere will now and then fall upon solutions to cancer control; or
3. What is obvious, we are going to have to settle down to working directly with each other with give and take, planning a sensible, deliberate path toward conquering the varieties of disease we label cancer and, from my point of view, especially ovarian cancer, for this multifaceted "disease" has so many similarities to other malignancies that the multifarious therapy which may result from planned and organized research should be able to be applied successfully by multifarious therapists to the other malignancies that plague mankind.

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COMBINATION OF CONSERVATIVE SURGERY AND IRRADIATION FOR CANCER OF THE BREAST*

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ABSTRACT:

In patients with relatively advanced local or axillary disease, or both, a simple mastectomy followed by irradiation gives the best local and regional control rates.

From the existing data, one can state unreservedly that women with early breast cancer take no chance on their life by having a treatment method which preserves the breast. In conjunction with the wedge excision, even if the axilla is clinically negative, a dissection of the low and central axilla brings enough information to decide on elective chemotherapy.

THE modalities of treatment for breast cancer must not only be evaluated by survival rates but also by local and regional control of the disease. The incidence of recurrences on the chest wall, in the regional lymphatics, or both, has been well correlated with the clinical features of cancer in the breast and in the axilla so that the management can be tailored with those clinical features in order to obtain maximum control of the disease.

CONTROL OF SUBCLINICAL DISEASE BY IRRADIATION

Subclinical disease is not only microscopic disease but disease which cannot be seen nor palpated. For instance, an aggregate of cancer cells (10^6 cells), 1 mm in diameter, is not microscopic but would not be felt in the axilla, and if felt under the skin in the supraclavicular area, it would be considered clinically positive. From the series of biopsied internal mammary lymph nodes, extended radical mastectomies, or both, it has been shown that at least 90 percent of the invaded internal mammary chains were positive at the microscopic level or with very small aggregates of cancer cells.[8,10,19] Because of well-established data on the frequency of invasion of the axilla, supraclavicular area, and internal mammary chain, one can establish a correlation between dose and percentage of control. Table I shows at least 90 percent control of occult deposits with 4,500–5,000 rads given in five weeks in the axilla, supraclavicular and parasternal areas.

CORRELATION OF FAILURES IN BREAST CANCER WITH CLINICAL FEATURES OF THE DISEASE

With locally advanced breast disease, extensive involvement of the axillary lymph nodes, or both, recurrences on the chest wall are frequent (Table II).[9,17] The wide invasion of the dermis lymphatics goes beyond what can be resected even with a wide excision of the breast and skin grafting. Conversely, large masses are a cause of failure of radiation therapy. In order to control 2 to 3 cm lymph nodes clinically positive in the axilla, one must give doses of the order of no less than 7,000 rads (Table III). For breast masses of 2 to 5 cm, 7,000 rads produce a relatively low control rate; it requires doses of the order

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TABLE I

FIVE YEAR CONTROL OF SUBCLINICAL DISEASE WITH IRRADIATION IN BREAST CANCER

(Axillary, Supraclavicular, and Parasternal Areas)

	Axillary Recurrence	Supraclavicular Recurrence	Parasternal Nodule
Without Irradiation		Axilla+in the Surgical Specimen† 20–26 percent	Axilla+the Surgical Specimen‖ 9 percent Central or Inner Quadrants (25/264)
With Irradiation	2 percent* 1 failure with 5,000 rads/5 wk.‡	Axilla+in the Surgical Specimen 11–13 percent 3,500 rads/3 wk.† 1.5 percent 4,500–5,000 rads/5 wk.‡ 1.2 percent 5,000–5,500 rads/7 wk.§	Axilla+in the Surgical Specimen¶ 0 percent Central or Inner Quadrants (0/204) 4,500–5,000 rads/5 wk.

* 65 patients with locally advanced breast cancer and clinically negative axilla treated between January 1955 through December 1967. Corrected for 75 percent of the patients expected to have histologically positive lymph nodes.[8]

† Jackson, S. M. *Clin. Radiol.*, 1966, *17*, 107. Robbins, G. C. *et al. Surg., Gynec. & Obstet.*, 1966, *122*, 979.

‡ Fletcher, G. H. *Cancer*, 1972, *29*, 545.

§ Calle, R. *et al. J. Radiol. Electrol.*, 1973, *54*, 929.

‖ Urban, J. A. *Cancer*, 1952, *5*, 992.

¶ Nelson, A. J., and Montague, E. D. *J.A.M.A.*, 1975, *231*, 189.

From: Fletcher, G. H., and Shukovsky, L. J. *J. Radiol. Electrol.*, publication pending.

of 8,000 to 10,000 rads in ten to twelve weeks to obtain 75 percent control of masses this size in the breast (Table III).[6,21] These doses are associated with subsequent fibrosis which at times can be crippling.

The usual situation, with few exceptions, is that the largest mass is in the breast and the next largest mass is in the low and central axilla (Fig. 1). Surgical excision and irradiation are complementary to secure freedom from disease in the local and regional areas. In patients who have had a radical mastectomy followed by elective chest wall irradiation because of invasion into the axilla, grave signs, or both, there is a lower incidence of chest wall recurrence than in those treated with surgery only for a similar degree of advancement of the disease (Table II). The Table also shows that for advanced disease of the same order as in the series published by Haagensen and Stout[9] and Spratt,[17] simple mastectomy alone, if the axilla is clinically negative, or with excision of clinically positive axillary lymph nodes, produces even better results, the incidence of chest wall recurrences being only 3.5 percent (Table IV). The thinning of the flaps in the radical mastectomy removes fat but does not remove the microscopic disease in the dermis lymphatics. The radical procedure actually makes irradiation less effective because the vascular supply is disturbed, resulting in some hypoxia of the tissues of the chest wall. Furthermore, with the simple mastectomy, irradiation is started two to three weeks after surgery, whereas, after a radical mastectomy, irradiation is delayed four to six weeks and not uncommonly as long as three months. Irradiation of the chest wall cannot be started prior to wound healing, since it results in an increased incidence of necrosis.

The techniques for irradiation of peripheral lymphatics and the chest wall after a radical mastectomy or a simple mastectomy have been described in detail.[5]

RADIATION THERAPY AND WEDGE EXCISION

There are several series reporting patients with early breast cancer and clinically negative axilla treated with irradiation after excision biopsy with ten year sur-

TABLE II

CHEST WALL RECURRENCES IN CANCER OF THE BREAST WITH LOCALLY ADVANCED DISEASE, EXTENSIVE AXILLARY INVOLVEMENT, OR BOTH

	Extensive Axillary Involvement	Locally Advanced Breast Lesion	>20 Percent Positive Axillary Lymph Nodes, Grave Signs, or Both	Locally Advanced,* Extensive Axillary Involvement, or Both
	percent	percent	percent	percent
Spratt Radical Mastectomy Only	45†	33†		
Haagensen Radical Mastectomy Only		47‡		
Haagensen Radical Mastectomy Only	35–40§			
MDAH Radical Mastectomy and 5,000 rads to Peripheral Lymphatics and Chest Wall			10	
MDAH Simple or Extended Simple Mastectomy and Irradiation 5,000 rads/5 weeks				3.5*

* The lesions were technically suitable for radical mastectomy. At least one of the following clinical features were present:

Primary: >5 cm—less than ½ breast
Edema or peau d'orange or wheals <½ breast
Central satellite nodules
Erythema <½ breast
Axillary Lymph Nodes: Multiple or chain
≤3 cm

† Number of lymph nodes involved not specified.
Spratt, J. S. *Cancer*, 1967, *20*, 1051.
‡ Haagensen, C. D., and Stout, A. P. *Ann. Surg.*, 1942, *116*, 801.
§ In 17 Stage A and 33 Stage B with 8 or more positive axillary lymph nodes.
Haagensen, C. D. Diseases of the Breast. 2nd Edition. W. B. Saunders Co., Philadelphia, 1971.
Modified from: Fletcher, G. H., and Shukovsky, L. J. *J. Radiol. Electrol.*, publication pending.
MDAH= M. D. Anderson Hospital.

vival rates of at least 70 percent,[1,14,15,20] equal to the survival rates reported with radical mastectomy for a similar stage of the disease. At M. D. Anderson Hospital, 82 patients with breast cancers which were small have been treated with wedge excision followed by 5,000 rads in five weeks to the breast, axilla, supraclavicular area, and internal mammary chain. A boost of 1,000 to 2,000 rads has been given through an appositional field when the axilla was clinically positive. The local and regional control rate is excellent (Table v) and should stay high despite a lack of long follow-up in all patients, since 75 percent local and regional recurrences appear by two years and only five percent appear after five years. Only four patients have experienced distant metastases. This small series shows that with careful selection, women do not take a chance on their life with a treatment aimed toward conservation.

IMMUNOSUPPRESSION

Table vi gives the ten year survival rates of 246 patients treated with radical mastectomy alone and of 419 treated with pre-

TABLE III

LOCAL AND AXILLARY FAILURES WITH IRRADIATION ONLY

		Recurrence in Axilla	Recurrence in Breast
		percent	percent
Fletcher	(1972)*		
Clinically Positive Axillary Lymph Nodes			
2–3 cm	7,000 rads/7 wk.	6†	
Calle	(1973)‡		
Size of Primary			
2–5 cm	7,000–8,000 rads/8–9 wk.		35
>5 cm	7,000–8,000 rads/8–9 wk.		68
>5 cm	8,000–9,000 rads/8–10 wk.		44
Zimmerman	(1966)§		
Size of Primary			
>5 cm	8,000–10,000 rads/10–12 wk.		28

* Fletcher, G. H. *Cancer*, 1972, *29*, 545.

† Corrected for 90 percent of lymph nodes expected to be histologically positive.[8]

‡ Calle, R., *et al.* *J. Radiol. Electrol.*, 1973, *54*, 929.

§ Zimmerman, K. W. *Cancer*, 1966, *19*, 67.

Modified from: Fletcher, G. H., and Shukovsky, L. J. *J. Radiol. Electrol.*, 1975, *56*, 383.

operative irradiation. Although 29 percent of the patients receiving preoperative irradiation had axillary metastases in the surgical specimen and, therefore, would be expected to have a poorer prognosis than the radical mastectomy alone group with only nine percent axillary metastases, the ten year results in the two groups are the same. This suggests that irradiation cured a percentage of patients since, in all series reported, the survival rates decrease with an increased percentage of patients having involvement of the axillary lymph nodes. The patients who received preoperative irradiation had a large volume of tissue irradiated. This does not substantiate the fear that irradiation might increase the probability of distant metastases by immunosuppression.

DISCUSSION

Objections to conservative surgery and irradiation have been made because of the relatively high local and regional failure rates experienced in other series. In a randomized series of radical mastectomy *versus* simple mastectomy and irradiation in Edinburgh, a local recurrence rate of 30 percent was seen.[2] In the Edinburgh series, the over-all tissue dose was 3,750 roentgens in the kilovoltage range.[12] At Guy's Hospital, in a randomized series of radical mastectomy *versus* "tylectomy" and irradia-

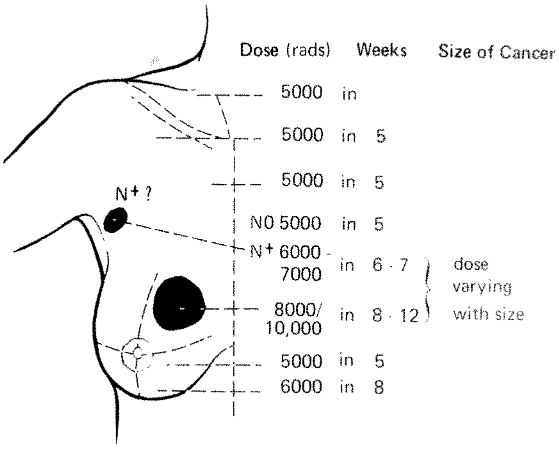

FIG. 1. Irradiation of breast cancer if gross masses have not been removed. As a rule, the largest mass is the primary tumor, the next largest are axillary lymph nodes; the supraclavicular lymph nodes, if palpable, are usually small. Five thousand rads in five weeks are given to clinically negative regional lymphatics. Added doses, graded to the size of the masses, are given through reduced portals to clinically positive axillary lymph nodes and to the primary tumor in the breast. (Modified from: Calle, R., Fletcher, G. H., and Pierquin, B. *J. Radiol. Electrol.*, 1973, *54*, 929–938.)

Table IV

LOCAL AND REGIONAL FAILURES IN PATIENTS WITH BREAST CANCER,* SIMPLE OR EXTENDED SIMPLE MASTECTOMY AND IRRADIATION,† 1964 THROUGH 1970

(Analysis August 1974)

Site of Recurrence	Total Mastectomy (60 patients) Clinically−Axilla	Extended Total Mastectomy‡ (29 patients) Clinically+Axilla	Percent
Chest wall	2	1	3.5
Axilla	1	0	1
Supraclavicular	0	0	0
Internal mammary chain	0	1	1
Total Recurrences	3	2	5.6 (5/89)

* The lesions were technically suitable for radical mastectomy. At least one of the following clinical features was present:

Primary: >5 cm—less than ½ breast
Edema or peau d'orange or wheals <½ breast surface
Central satellite nodules
Erythema <⅓ breast
Axillary Lymph Nodes: Multiple or chain
≤3 cm

† 5,000 rads in 5 weeks.

‡ Simple excision of clinically positive axillary lymph nodes.

From: Fletcher, G. H., and Skukovsky, L. J. *J. Radiol. Electrol.*, 1975, *56*, 383.

tion, a 20 percent local and regional recurrence rate was seen in Stage I cases (axilla clinically negative) and 70 percent in Stage II cases (clinically positive axilla).[1] In the Guy's Hospital series, with megavoltage treatment, 2,500–2,700 rads in twelve days were given to the axilla, in patients with either clinically negative or positive axillae, and 3,500–3,800 rads in three weeks to the chest wall. In other series with doses of 4,500 rads in four weeks[14] and 6,500–7,000 rads in seven weeks,[3] a ten percent recurrence rate in the breast has been experienced. At M. D. Anderson Hospital, with meticulously designed portals and a tissue dose of 5,000 rads, at least 95 percent local and regional freedom from disease is obtained, both in the patients treated with

Table V

EXCISION AND IRRADIATION FOLLOW-UP, AUGUST 1961 THROUGH DECEMBER 1974

(Analysis—April 1975)

	No. of Patients	6–12 Months	13–24 Months	25–36 Months	37–48 Months	49–60 Months	61–120 Months	>120 Months
Clinically negative axilla								
NED	60	12	19*	6	9	9	3	2
Alive—DM	2	1					1	
Dead	7	1—ID		1—DM	3—ID		2—ID	
Clinically positive axilla								
NED	11	2	2	1	2		2	2
Dead	2	1—DM					1—ID	

* Two patients with recurrences: 1—Axilla at 12 months treated with radical mastectomy. NED 24 months after the surgical procedure; 1—Breast at 10 months treated with radical mastectomy. NED 18 months after the surgical procedure.

NED = no evidence of disease.
DM = distant metastases.
ID = intercurrent disease.

TABLE VI

TEN YEAR SURVIVAL IN TWO RADICAL MASTECTOMY SERIES AT M. D. ANDERSON HOSPITAL*
JANUARY 1955 THROUGH DECEMBER 1967

	No. of Patients	Percent of Axillary Nodes Histologically Positive	Percent
Radical Mastectomy Only†	246	9	63
Irradiation (Peripheral Lymphatics and Breast) + Radical Mastectomy	419	29	62

* Age adjusted survival rate—Berkson-Gage.

† These patients had primary lesions located in the outer half of the breast with histologically negative axilla. The 9 percent who had positive axillary lymph nodes should have had postoperative irradiation, but, for a variety of reasons, did not.

Adapted from: Fletcher, G. H. Textbook of Radiotherapy. Second edition. Lea & Febiger, Philadelphia, 1973.

simple mastectomy and irradiation, and in the patients treated with wedge excision and irradiation.

Recent tentatively favorable results with elective chemotherapy in patients having four or more positive axillary lymph nodes in the specimen suggest that one may add elective chemotherapy to prevent the growth of distant metastases which are left untouched by the local and regional treatment. If a dissection limited to the low and central axilla recovers a small number of negative lymph nodes, there must be minimal invasion, since it has been demonstrated[10] that if the low and central axilla is negative, the apex of the axilla is practically never involved.

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SQUAMOUS CELL CARCINOMA OF THE ORAL • TONGUE AND FLOOR OF MOUTH[*]

EVALUATION OF INTERSTITIAL RADIUM THERAPY

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ABSTRACT:

From January, 1965, to December, 1972, 46 patients with squamous cell carcinoma of the floor of the mouth and 102 patients with squamous cell carcinoma of the oral tongue were treated at M. D. Anderson Hospital and Tumor Institute by interstitial irradiation alone or in combination with external irradiation. Through the years the combination of radiation therapy modalities has been adjusted in an attempt to improve local control, keeping complications to a minimum.

In this paper we analyze local control, causes of failure and complications as related to the primary size (T Stage) and radiation therapy techniques employed.

THE purpose of this paper is to analyze the failures at the primary site, soft tissue ulcers, and bone necrosis as related to the size of the primary tumor (T Stage) and modality of radiation technique employed in a group of patients who had an interstitial implant as part of the treatment for the primary lesion. Although the management of the primary lesion and of the regional metastases in the neck are interrelated therapeutic problems, no attempt will be made to analyze the neck results.

MATERIAL

From January, 1965 to December, 1972, 46 patients with squamous cell carcinoma of the floor of the mouth and 102 patients with squamous cell carcinoma of the oral tongue were treated at M. D. Anderson Hospital and Tumor Institute by interstitial irradiation alone or combined with external irradiation. The analysis was made in March, 1975 and, therefore, all patients have a minimum of a two year follow-up which is adequate for evaluation of results at the primary site. An additional 28 patients with floor of the mouth and 17 patients with oral tongue T_1 to T_3 lesions were treated by external irradiation alone. Most of these patients had lesions involving more than half of the tongue or massively involving the floor of the mouth, but a few early lesions were also treated by external beams only, based on contraindication for general anesthesia. During the same period of time, 118 patients with a floor of mouth lesion and 135 patients with an oral tongue lesion were treated by surgery.

The staging for the primary lesion is as follows:

- T_1—Tumors less than 2 cm in diameter
- T_2—Tumors 2 to 4 cm in diameter, limited invasion of surrounding structures
- T_3—Tumors more than 4 cm in diameter, or having invasion of surrounding structures (periosteal involvement—"pressure" defect in bone), or both
- T_4—Massive tumor or bone invasion

The techniques of implantation for these two anatomical areas have been described in detail.[3]

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TABLE I

SQUAMOUS CELL CARCINOMA OF THE FLOOR OF MOUTH (ANALYSIS MARCH, 1975)
INTERSTITIAL IRRADIATION ALONE OR WITH EXTERNAL IRRADIATION

Stage	Number of Patients Treated	Radium Alone	2,000 rads External in 5–6 Days*	5,000 rads External in 5 Weeks†	Unusual Treatment‡
T_1	10	3	0	2	5
T_2	24	2	1	14	7
T_3	9	0	0	4	5
T_4	3	0	0	2	1
Total	46	5	1	22	18

* Single ipsilateral field.
† Single ipsilateral 22 MeV photon or parallel opposed Co^{60} fields.
‡ Submental and/or intraoral electron beam fields.

BACKGROUND

Uneven distribution of the needles is the rule in large implants even in the most skillful hands. Since the combination with external irradiation buffers the swing of dose within the implant,[4] half external and half interstitial irradiation had always been used for late T_2, T_3, and some T_4 lesions. From January, 1965, the treatment policy for lesions of the oral tongue and floor of the mouth was modified for all lesions by using external irradiation prior to the implant except for the very early lesions in patients with a clinically negative neck. An added reason to use external irradiation first was the suggestion in a few patients that tumor cells driven by the needles had been producing a recurrence at some distance from the primary site. The data showing that elective irradiation of the neck lymphatics in squamous cell carcinomas of the upper respiratory and digestive tract is effective,[5] increased the indications to irradiate the lymphatic areas when there is a significant probability of invasion.

When an early lesion could be covered by a small-sized implant, 2,000 rads tumor dose has been given with external irradiation as a preneedling dose in five or six treatments encompassing also the first relay of regional lymphatics, *i.e.*, the submaxillary triangle and subdigastric lymph nodes.[6] In moderate-sized lesions and in those located so that a good geometric implant would be unlikely, 5,000 rads midline tumor dose in five weeks has been given first with external irradiation. Low dosage rates were obtained by using low linear intensity needles, 0.5 and 0.66 mg/cm for single plane implants and 0.25 and 0.33 mg/cm for double and triple plane implants or volume implants.

When computer dosimetry became available in 1961, a generous minimal tumor dose was selected from the isodoses knowing that the doses could be as much as 20 percent higher than the doses given in earlier years. When an analysis in January, 1963, showed an increased incidence of complications, the doses were reduced by ten percent by taking a less generous minimum tumor dose. During the following two years (1963 and 1964), there was a decrease in complications, but an increase in recurrences in patients with an oral tongue lesion, but not in those with a floor of the mouth lesion.[2] Since 1965, lesions treated by interstitial radium or iridium alone have received doses from 6,000 rads in 120 hours to 7,000 rads in 175 hours for floor of the mouth lesions and 5,800 rads in 46 hours to 7,000 rads in 175 hours for oral tongue lesions. After 2,000 rads with the external beam in five or six treatments the dose was 5,000 rads in 166 hours for one case of floor

TABLE II

SQUAMOUS CELL CARCINOMA OF THE FLOOR OF MOUTH (ANALYSIS MARCH, 1975)
INTERSTITIAL IRRADIATION ALONE OR WITH EXTERNAL IRRADIATION

Stage	Number of Patients Treated	Recurrences	Recurrences Salvaged By Surgery	Ultimate Local Failures
T_1	10	3*	2/3†	1/10
T_2	24	3	1‡/3	2/24
T_3	9	1	0/1	1/9
T_4	3	2	0/2	2/3
Total	46	9	3/9†	6/46

* Unusual treatments (gold grain implants)+submental electron beam fields in one patient because of trismus (previous squamous cell carcinoma of the oropharynx); in the other two because of contraindication to general anesthesia.

† One-third was salvaged by radium implant following a second recurrence after excision and skin graft for the first recurrence.

‡ Too early to determine result following surgery.

of the mouth and varied from 4,200 rads in 70 hours to 5,600 rads in 140 hours for oral tongue lesions. After 5,000 rads in five weeks with external beam, the radium dose has been 2,500 to 3,000 rads in 72 to 100 hours for floor of the mouth and 2,500 to 3,000 rads for oral tongue lesions in 42 to 100 hours.

RESULTS

FLOOR OF THE MOUTH

Table 1 shows the modalities of irradiation used according to the T stage of the primary lesion of the floor of the mouth. The choice of treatment has been based on subtle reasons. It is to be noted that only five of 34 patients with Stages T_1 and T_2 lesions were treated by interstitial irradiation alone. Tumors of the floor of the mouth extend to the submucosal tissues of the submental and submandibular areas, the periosteum of the mandible, and the muscles of the tongue; and therefore external irradiation was given before implantation in the majority of patients. Eighteen of the 46 (T_1 to T_4) were treated by unusual treatment modalities employing a submental electron beam field or a submental and lateral field plus the implant in an attempt to diminish the amount of radiation going through the mandible or trying to avoid an area previously treated for another primary

TABLE III

SQUAMOUS CELL CARCINOMA OF THE FLOOR OF MOUTH (ANALYSIS MARCH, 1975)
INTERSTITIAL IRRADIATION ALONE OR WITH EXTERNAL IRRADIATION

Stage	Number of Patients Treated	Soft Tissue Ulcers	Healed By Conservative Treatment	Still Present	Treated Successfully By Surgery
T_1	10	1/7	1/1	—	—
T_2	24	3/21	2/3	1/3	—
T_3	9	4/8	2/4	—	2/4
T_4	3	0/1	—	—	—
Total	46	8/37*	5/8†	1/8	2/8†

* Patients without recurrence.

† 7/8 Healed.

TABLE IV

SQUAMOUS CELL CARCINOMA OF THE FLOOR OF MOUTH (ANALYSIS MARCH, 1975)
INTERSTITIAL IRRADIATION ALONE OR WITH EXTERNAL IRRADIATION

Stage	Number of Patients Treated	Osteonecrosis	Healed By Conservative Treatment	Still Present	Treated Successfully By Surgery
T_1	10	1/7	1/1	—	—
T_2	24	5/21	2/5	—	3/5
T_3	9	2/8	—	1/2	1/2
T_4	3	0/1	—	—	—
Total	46	8/37*	3/8†	1/8	4/8†

* Patients without recurrence.
† 7/8 Healed.

lesion. Some superficial lesions in edentulous patients, in whom the floor of the mouth was relatively flat, were treated by intraoral cones plus an interstitial implant. Sixteen of 34 T_1 and T_2 lesions and 4/9 T_3 lesions receive 5,000 rads in five weeks generally with parallel opposed fields followed by an interstitial implant.

Table II shows the recurrence rates, the number of recurrences salvaged by a surgical procedure, and the ultimate failure rates. There are three recurrences among T_1 lesions; all three were treated by unusual modalities, one patient was unable to open the mouth because of trismus caused by previous treatment for a squamous cell carcinoma of the oropharynx and was treated with submental electron beam field plus a gold grain implant; the other two patients were implanted with gold grains because of medical contraindication for general anesthesia. Gold grain implants are more subject to cold spots than radium or iridium implants. The control rates in the T_2 and T_3 lesions are excellent.

Table III shows that the incidence of soft tissue necrosis is the same for T_1 and T_2 and higher for T_3 lesions. In Table IV we see that osteonecrosis is less common in T_1 lesions where lesser amounts of external irradiation were used and has about the same incidence for T_2 and T_3 lesions where most of the patients received large amounts of external irradiation.

It is to be noted that final healing of both soft tissue necrosis and bone necrosis is

TABLE V

SQUAMOUS CELL CARCINOMA OF THE ORAL TONGUE (ANALYSIS MARCH, 1975)
INTERSTITIAL IRRADIATION ALONE OR WITH EXTERNAL IRRADIATION

Stage	Number of Patients Treated	Radium Alone	2,000 rads External in 5–6 Days*	5,000 rads External in 5 Weeks†	Unusual Treatment‡
T_1	18	8	6	3	1
T_2	57	2	30	18	7
T_3	27	1	0	23	3
Total	102	11	36	44	11

* Single ipsilateral field.
† Single ipsilateral 22 MeV photon or parallel opposed Co^{60} fields.
‡ Submental and/or intraoral electron beam fields.

Table VI

SQUAMOUS CELL CARCINOMA OF THE ORAL TONGUE (ANALYSIS MARCH, 1975)
INTERSTITIAL IRRADIATION ALONE OR WITH EXTERNAL IRRADIATION

Stage	Number of Patients Treated	Recurrences	Recurrences Salvaged By Surgery	Ultimate Local Failures
T_1	18	1*	1/1	0/18
T_2	57	6	4/6	1/57
T_3	27	6	1/6	5/27
Total	102	13	6/13	6/102

* 2,000 rads/5 days+radium (5,200 rads/120 hours). Recurrence at 2 years (primary+neck)———→surgery and postoperative irradiation. No Evidence of Disease (   ).

outstanding (85 percent). Twenty-five percent of the patients with soft tissue necrosis and 50 percent of those with bone necrosis required surgical procedures.

ORAL TONGUE

Table v shows the modalities of irradiation used for different stages of the disease in lesions of the oral tongue. The choice of radiation treatment modality has been based mainly on the size of the primary lesion and the presence of neck lymph nodes. In addition, attention was paid to extension or possible extension to the floor of the mouth, the glossopalatine sulcus, and the base of the tongue. Fourteen of 18 patients with T_1 lesions had relatively limited or moderate lesions with no clinically positive lymph nodes and were treated by radium alone or with 2,000 rads tumor dose in five or six treatments before the implant. Half of the patients with T_2 lesions were treated in the same fashion because of limited or moderate lesions and no clinically positive lymph nodes, but 18 of 57 patients received a 5,000 rad tumor dose in five weeks which encompassed at least the primary and the first lymphatic relay. Most T_3 lesions were treated before needling with 5,000 rads tumor dose in five weeks. A limited number of patients (11/102) were treated by unusual modalities of irradiation, mainly with submental fields or combining one lateral field and a submental field; these were mainly lesions of the undersurface of the tongue, and an attempt was made to minimize irradiation of the mandible; when bone has been extensively irradiated defense mechanisms are poor. External irradiation was

Table VII

SQUAMOUS CELL CARCINOMA OF THE ORAL TONGUE (ANALYSIS MARCH, 1975)
INTERSTITIAL IRRADIATION ALONE OR WITH EXTERNAL IRRADIATION

Stage	Number of Patients Treated	Soft Tissue Ulcers	Healed By Conservative Treatment	Still Present	Treated Successfully By Surgery
T_1	18	4/17	3/4	1/4	—
T_2	57	12/51	10/12	2/12	—
T_3	27	3/21	2/3	—	1/3
Total	102	19/89*	15/19†	3/19	1/19†

* Patients without recurrence.
† 15/19 Healed.

TABLE VIII

SQUAMOUS CELL CARCINOMA OF THE ORAL TONGUE (ANALYSIS MARCH, 1975)
INTERSTITIAL IRRADIATION ALONE OR WITH EXTERNAL IRRADIATION

Stage	Number of Patients Treated	Osteonecrosis	Healed By Conservative Treatment	Still Present	Treated Successfully By Surgery
T_1	18	3/17	2/3	1/3	—
T_2	57	9/51	5/9	1/9	3/9
T_3	27	5/21	1/5	1/5	3/5
Total	102	17/89*	8/17†	3/17	6/17†

* Patients without recurrence.
† 14/17 Healed.

followed by an interstitial needling (radium or iridium wire) through the dorsum of the tongue.

Table VI shows the recurrence rates, the number of recurrences salvaged by surgery, and the ultimate failure rate. The failures are low and the ultimate failure rates are excellent for T_1 and T_2 lesions and still very good for T_3 lesions.

Tables VII and VIII show that the incidence of soft tissue necrosis and osteonecrosis is the same for T_1 to T_3 lesions.

The final healing of both soft tissue necrosis and bone necrosis is outstanding (80 to 85 percent), five percent of the patients with soft tissue necrosis and 35 percent of those with bone necrosis requiring surgical procedures.

DISCUSSION

The control rates for squamous cell carcinoma of the floor of the mouth and the oral tongue are excellent. In the T_1 cases, the choice of technique was not optimal in three cases for medical or technical reasons, as discussed previously.

The over-all incidence of soft tissue necrosis has diminished dramatically since 1965. A recent report shows that since July, 1969, there has been a 60 percent reduction in bone necrosis as compared with before 1969.[1] This reduction is due to a very conservative approach and the recognition by the dental service that fairly good teeth should not be extracted prior to nor after radiation therapy. Spontaneous osteoradionecrosis, when surgical manipulations are avoided, can be reduced to a minimum when good conservative oral hygiene is established.

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COMBINED RADIATION THERAPY AND 5-FLUOROURACIL FOR ADVANCED SQUAMOUS CELL CARCINOMA OF THE ORAL CAVITY AND OROPHARYNX: A RANDOMIZED STUDY*

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ABSTRACT:

In 1961, a randomized study was begun at the University of Wisconsin Medical Center in which the treatment of advanced squamous cell carcinoma of the head and neck with radiation therapy was compared with combined treatment with radiation therapy and 5-Fluorouracil. One hundred and thirty-six patients with primary lesions in the oral cavity, the base of the tongue, and the oropharynx were analyzed. Both local control and survival were better in the combined treatment group than in the group with radiation therapy alone. However, in only the oral cavity patient population was the difference statistically significant. Both acute and late complications were also increased in this group of patients who received combined treatment.

IN 1961 a randomized study was begun at the University of Wisconsin Medical Center in which the treatment of advanced squamous cell carcinoma of the head and neck with radiation therapy was compared with combined treatment with radiation therapy and the administration of 5-Fluorouracil (5-FU) systemically. Gollin *et al.*[11] reported the initial results of this study previously and noted that there was a significant increase in the mean length of survival from 16 months to 32 months when 5-FU was combined with radiation therapy for lesions of the oral cavity, including the base of tongue. There was also an increase, but not statistically significant, in the mean length of survival for the combined therapy in patients with oropharyngeal lesions. However, no increased survival was noted in a small group of patients with disease in the larynx, hypopharynx, and nasopharynx. This study has been continuing and the purpose of this report is to update the previous results and to analyze the data with respect to local control, complications, and the development of metastasis in patients with advanced carcinoma of the oral cavity and oropharynx.

PATIENT SELECTION AND TREATMENT METHODS

The patients were selected and treated as previously reported.[11] Briefly, patients with advanced squamous cell carcinoma of the oral cavity or oropharynx who had no clinical evidence of metastasis beyond regional neck lymph nodes were eligible for the study. In the present report, the oral cavity includes the anterior two-thirds of the tongue, alveolar ridge, floor of the mouth, and buccal mucosa; and the oropharynx includes primarily the tonsillar

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TABLE I

TNM STAGING-GROUPING SYSTEM

T_1:	Tumor less than 2 cm in diameter
T_2:	Tumor 2 to 4 cm in diameter without invasion of surrounding structures
T_3:	Tumor greater than 4 cm in diameter or with invasion of surrounding structures
T_4:	Massive tumor or tumor with bone involvement
N_0:	Regional lymph nodes not palpable
N_1:	Single homolateral lymph node, movable and less than 3 cm in diameter
N_2:	Movable lymph node greater than 3 cm in diameter or multiple homolateral lymph nodes, not fixed
N_3:	Fixed, bilateral or contralateral lymph node(s)
M_0:	No clinical evidence of distant metastasis
M_1:	With clinical evidence of distant metastasis

Stage I:	T_1	N_0	M_0
Stage II:	T_2	N_0	M_0
Stage III:	T_3	N_0	M_0
	Any T	N_1 or N_2	M_0
Stage IV:	All other cases		

fossa, pillars, and soft palate. Staging used was a TNM system as shown in Table I.

Patients were randomized to receive either radiation therapy alone or radiation therapy combined with 5-FU as previously described.[11] From 1961 through 1973, a total of 163 patients with advanced carcinoma of the oral cavity or oropharynx entered into the study and 151 patient-records were reviewed for this report. Twelve cases were excluded because three patients in the radiation therapy alone group and four in the combined treatment group did not complete therapy, and five charts contain inadequate data for this analysis.

Prior to 1964, patients were treated with a 1,000 Kvp Maxitron x-ray therapy unit with a half-value layer of 9 mm of copper at a focal-skin distance of 70 cm. After that date patients were treated with a 5,000 to 10,000 Curie source Cobalt 60 unit at a source-skin distance of 80 cm. More recently, patients have been treated with a Varian 4 MeV linear accelerator at a source-skin distance of 80 cm. The minimum radiation dose to the primary lesion was 6,000 to 7,000 rads in 6 to 10 weeks.

Initially, lateral parallel opposed portals were used to cover the primary lesion and the associated lymphatics. After 5,000 rads, gross remaining lymph node disease was treated either by a booster dose to the primary lesion to an additional 1,000 to 2,000 rads or by radical neck dissection. The dose and method of radiation therapy were similar in all patients, whether concomitant 5-FU was administered or not.

In patients who received combined therapy, 5-FU was given intravenously at a dose schedule of 10 mg per kilogram of body weight per day for the first three days of the course of radiation therapy. Five mg per kilogram were administered on the fourth day and then on Mondays, Wednesdays and Fridays until the end of radiation therapy, unless severe local toxicity developed.

During the earlier years of this study, a certain number of patients received intra-arterial infusion of 5-FU prior to randomization. However, it was soon noted that survival was not increased with the addition of this treatment modality and it was abandoned.[10]

RESULTS

Patients in the combined treatment groups uniformly developed more severe acute mucosal reactions. Many required hospitalization and supportive care, including nasogastric feeding tube, during the treatment course.

In order to update the previously reported results, we first plotted the over-all survival of the two treatment groups of the entire patient population studied as shown in Figure 1 ($N = 151$). The Kaplan-Meier statistical procedure[15] was utilized to include patients who died from all causes. Comparison of the two curves by the Gehan's test[6] reveals that the survival of the combined treatment group is significantly better than that of the group that received radiation therapy alone ($P < .05$). Note that the survival curves separated as early as in the first year and they became parallel after 24 months. After this time, the slope of these curves undoubtedly reflects only a normal attrition of both groups of patients which would be seen in the general population who are in this age group.

The patients were also considered according to the three primary sites of involvement: (1) oral cavity; (2) base of tongue; and (3) oropharynx, *i.e.*, primarily lesions of the tonsillar fossa, pillars and soft palate, with or without extension to the pharyngeal wall. Figure 2 illustrates the survival of the two treatment groups for oral cavity lesions. Note that survival is significantly better for those patients who received concomitant 5-FU than for those who received radiation therapy alone. Although for oropharyngeal lesions the survival curves show that the combined treatment is better (Fig. 3), the difference is not statistically significant.

After eliminating all T_2N_0 patients who were included in the previous report and five patients who have been followed for less than two years, there was a total of 136 patients available for the remaining analysis of this study. Tables II and III show the distribution of these two treatment groups by TNM status, respectively. Thus, all of them had either Stage III or Stage IV disease and all were followed for a minimum of two to a maximum of 13 years. Sex and age distributions of both treatment groups are shown in Figure 4.

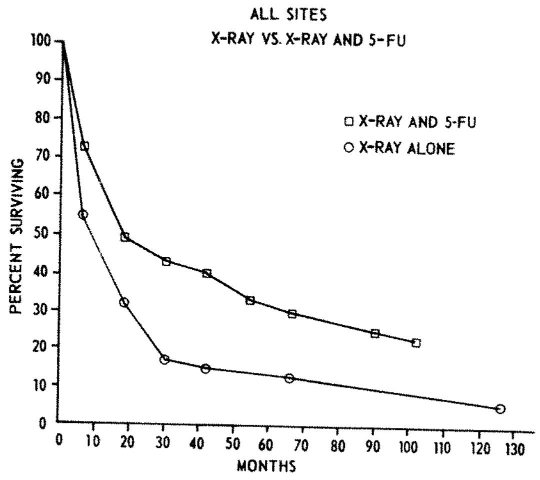

Fig. 1. Survival curves of the two treatment groups of the entire patient population studied, computed by the Kaplan-Meier procedure.[15] $p<.05$.

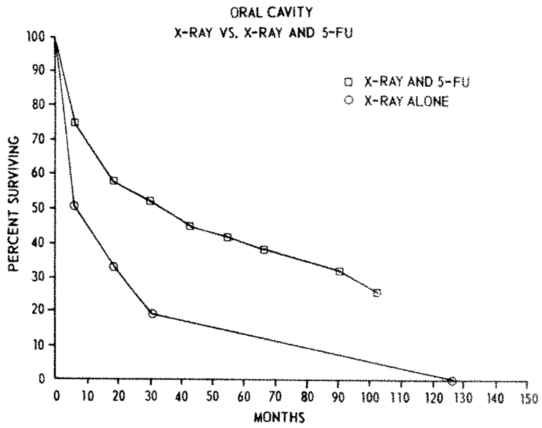

Fig. 2. Survival curves of the two treatment groups in patients with oral cavity lesions, computed by the Kaplan-Meier procedure.[15] $p<.05$.

Since all but two recurrences appeared by the end of the second year, we consider the recurrence-free rate at 24 months an indicator of local control. We first compared those patients who received intra-arterial 5-FU prior to randomization with those who did not. As shown in Table IV the NED (no evidence of disease) rates at two years are apparently not increased by the addition of this modality of therapy, as previously reported.[10] Table V shows the NED rates of the two treatment groups for lesions of the three different primary sites. When all these sites are combined and compared, the NED rate at two years for those treated with combined therapy is significantly better than that for the group treated with radiation therapy alone ($P <.05$). Looking at the individual sites, again the local control is superior in the groups that received combined therapy; although the patient number in the base of the tongue group is perhaps too small to permit meaningful conclusions in that particular group.

Also of possible interest with respect to lymph node status in all these areas of primary involvement is that the presence or absence of lymph node metastasis did not

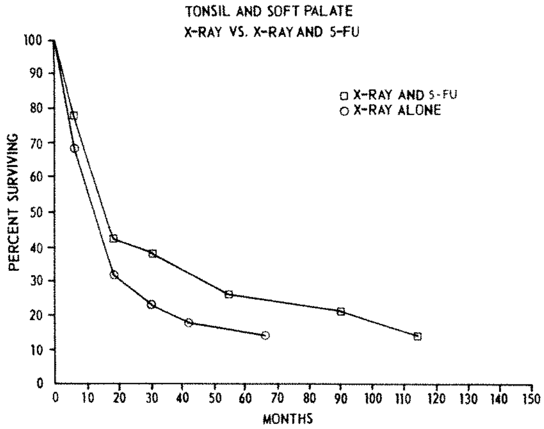

Fig. 3. Survival curves of the two treatment groups in patients with oropharynx lesions, computed by the Kaplan-Meier procedure.[15]

seem to influence the NED rate so much in the combined therapy groups as in the radiation therapy alone groups. This result was apparently not related to surgical intervention, since a retrospective analysis shows that frequencies of both planned radical neck dissection and neck surgery for residual disease were the same in both treatment groups (Table VI).

Table VII shows a breakdown analysis of patients with oral cavity lesions. It is noteworthy that the incidence of metastasis with the primary lesion controlled, and the development of second malignancies, were very similar between the two treatment groups. However, major complications were seen only in the group of patients who received combined therapy. We have defined a major complication as soft tissue or bone necrosis, or fistula formation in a patient who has the primary lesion controlled. Five patients developed major complications, but only one of them died due to a complication. Of the other four, two had successful excision and are alive with NED at seven and eleven years, respectively; one patient died of intercurrent disease and one patient healed spontaneously. The seven year survivor was a "surgical salvage" patient and surgery was most likely a contributing if not a causal factor to the development of fistula. Minor complications such as small ulcerations were seen in both groups with similar frequencies. These were usually associated with floor of mouth and alveolar ridge lesions and developed within the first year after completion of therapy. Four patients in each treatment

Table II

DISTRIBUTION BY TNM SYSTEM:
RADIOTHERAPY ALONE GROUP

$N=68$	N_0	N_1	N_2	N_3
T_1	0	0	0	1
T_2	0	2	0	2
T_3	15	11	1	7
T_4	7	6	0	16
Total	22	19	1	26

Table III

DISTRIBUTION BY TNM SYSTEM:
COMBINED THERAPY GROUP

$N=68$	N_0	N_1	N_2	N_3
T_1	0	0	0	0
T_2	0	4	1	2
T_3	16	9	2	10
T_4	4	5	1	14
Total	20	18	4	26

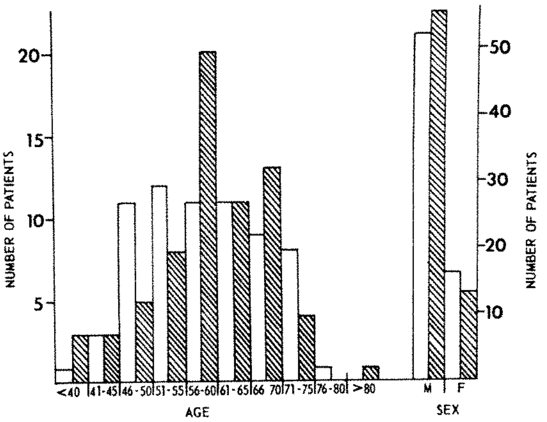

Fig. 4. Distributions of the two treatment groups of patients by age and sex. Blank columns: radiation therapy alone. Shaded columns: combined therapy.

group subsequently developed local recurrence and died.

During analysis of our data, we found eight patients in the radiation therapy alone group with mandibular involvement and none of them survived free of disease (NED) at two years; whereas none of the T_4 patients in the combined treatment group had bone involvement.

Similar results are seen in the groups of patients with oropharyngeal lesions with respect to incidence of metastasis and development of second malignant lesions (Table VIII). However, no major complications were encountered, even in the combined treatment group at this site.

DISCUSSION

In order to improve the results of either surgery or radiation therapy in the treatment of patients with advanced squamous cell carcinoma of the head and neck, a number of programs with combined chemotherapy and radiation therapy has been attempted. A recent review by Goffinet and Bagshaw[9] summarizes over six controlled clinical trials during the past decade. However, the only statistically significant results reported were those of the study initially reported by Ansfield *et al.*[1] and Gollin *et al.*[11]

TABLE IV

COMPARISON OF THE TWO YEAR NED RATES BETWEEN THE TWO TREATMENT GROUPS WITH RESPECT TO PRIOR THERAPY WITH INTRA-ARTERIAL INFUSION OF 5-FU

	Radiation Therapy	Combined
Oral Cavity		
With prior infusion	1/7	2/6
Without prior infusion	5/26	16/27
Base of Tongue		
With prior infusion	0/4	0/1
Without prior infusion	0/8	5/11
Oropharynx		
With prior infusion	2/7	3/4
Without prior infusion	4/16	7/19
N=136	12/68	33/68

Our present review substantiates these initial results that over-all survival of advanced lesions of the oral cavity and oropharynx is superior for combined 5-FU and radiation therapy (Fig. 1). However, when primary sites were separately analyzed, oral cavity is the only group for which the survival curves are statistically different (Fig. 2). The data in Tables VII and VIII indicate that although the addition of 5-FU improves the local control probability, there is no trend toward suppression of

TABLE V

COMPARISON OF THE TWO YEAR NED RATES BETWEEN THE TWO TREATMENT GROUPS WITH RESPECT TO LYMPH NODE STATUS

	Radiation Therapy		Combined	
	No.	Percent	No.	Percent
Oral Cavity				
Without lymph nodes	3/14	(21)	7/11	(64)
With lymph nodes	3/19	(16)	11/22	(50)
Base of Tongue				
Without lymph nodes	0/4	(0)	1/3	(33)
With lymph nodes	0/8	(0)	4/9*	(44)
Oropharynx				
Without lymph nodes	2/4*	(50)	3/6	(50)
With lymph nodes	4/19	(21)	7/17	(41)
N=136	12/68	(18)	33/68	(49) p<.05

* One patient from each of these two groups had recurrence after 24 months.

Table VI

FREQUENCY OF RADICAL NECK DISSECTION

	Radiation Therapy	Combined
Planned R.N.D. as part of therapy regimen	6/68	6/68
R.N.D. for residual neck disease after full course of radiation therapy	2/68	2/68

R.N.D. = Radical neck dissection.

distant metastasis.

While the survival rates of the radiation therapy alone groups in this study appear somewhat lower than those reported by some authors,[3,7,17] they compare closely to others.[4,5,8,20] The differences are perhaps due to such factors as staging systems, particularly with respect to the status of nodal involvement, and patient populations. Nevertheless, as a self-controlled study in this series, the effect of 5-FU does seem to be a real factor inasmuch as these other factors are comparable within our patient population groups. The main exception perhaps is the imbalance of numbers of T_4 patients with bone involvement between our two treatment groups. Whether or not these have affected our results cannot be determined. However, we suggest that bone involvement itself may not be a significant factor since Lampe[16] reported a 53 percent determinate five year survival rate in his series of 19 patients (all N_0) and many of them have an intact mandible and wear dentures today. Another possible factor would be hospitalization, since many of our patients in the combined treatment groups were hospitalized in order to complete therapy because of acute reactions. Again, whether or not this has affected our results cannot be evaluated. However, such influence would seem to be small, if present, since significant increase in survival was seen primarily in the oral cavity category, rather than a uniform improvement for all advanced head and neck lesions.

The metabolism and possible mechanism of action of 5-FU have been studied and reviewed by Heidelberger[12,13] and by Vermund and Gollin,[19] respectively. Although when 5-FU is given intra-arterially, significant but temporary regression of tumor mass is frequently observed,[14] the drug alone as was administered intravenously in the schedule and dosage of this study is not known to be effective in causing even a temporary tumor regression. When combined with ionizing radiation, however, radiobiological data demonstrate a con-

Table VII

ORAL CAVITY (1961–1972)

	Radiation Therapy		Combined	
Number of Patients	33		33	
Local Failure	25		17	
Died from disease		24		13
Surgical salvage		1		3
Radium implant salvage		0		1
Local Control (initial)	8		16	
Local Control (total)	9		20	
Metastasis		2		2
Intercurrent disease		2 (1)*		7 (2)*
Alive and well		5		11
Complications (major)	0		5	
(minor)	6		5	

* ( ) Indicates number of patients who died from a second malignancy.

Table VIII

OROPHARYNX (1961–1972)

	Radiation Therapy		Combined	
Number of Patients	23		23	
Local Failure	13		10	
Died from disease		12		10
Radium implant salvage		1		0
Local Control (initial)	10		13	
Local Control (total)	11		13	
Metastasis		4		3
Intercurrent disease		4 (2)*		5 (2)*
Alive and well		3		5
Complications	0		0	

* ( ) Indicates number of patients who died from a second malignancy.

centration dependent enhancement of the effect of radiation on both tissue culture and animal tumor systems.[2,12,18] Our clinical experience from this study concurs that 5-FU enhances the effect of radiation on both normal and tumor tissues locally, since both acute and late normal tissue reactions were increased and there was better local tumor control in the combined therapy groups.

The results of this study continue to be encouraging, although far from conclusive, indicating the need for further cooperative trials to include 5-FU and radiation therapy in regimens of treatment for advanced carcinomas of the oral cavity and possibly oropharynx.

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CARCINOMA OF THE OROPHARYNX[*]

RESULTS OF MEGAVOLTAGE RADIATION THERAPY IN 305 PATIENTS

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ABSTRACT:

Three hundred and five patients with oropharyngeal carcinomas received linear accelerator radiation therapy at the Stanford University Medical Center between 1956 and 1973. All were staged by the TNM system, using the UICC Classification of 1962. Actuarial five year survival for patients with tonsil cancers ranged from 50 percent to 18 percent for those with T_1 and T_3 lesions, respectively. Disease-free survival was higher than actuarial survival for patients with T_1 and T_2 lesions, reflecting an alteration of the latter curves by deaths from intercurrent diseases and second primary malignancies. Actuarial survival for patients with base of the tongue carcinomas was approximately 35 percent for those with T_1 and T_2 primary lesions and 22 percent for patients with T_3 carcinomas.

Considering all oropharyngeal sites of involvement together, clinically involved cervical lymph nodes were controlled by radiation therapy alone in 60 of 91 patients with N_1 nodal involvement (67 percent), in twelve of 25 with N_2 neck disease (48 percent) and in 46 percent of those patients with N_3 involvement (34 of 74). Eighty-nine percent of patients whose lymph nodes were not controlled by radiation therapy alone also had uncontrolled primary cancers. Over 90 percent of the patients whose cervical lymph nodes were initially uninvolved remained free of late nodal metastases if at least the regional (first echelon) lymph nodes were included in the primary treatment fields.

The results of a randomized trial which compared surgery and radiation therapy alone and the two modalities in combination for the treatment of a limited number of patients with advanced cancers of the oropharynx, supraglottic larynx and hypopharynx suggest that surgery alone is not the treatment of choice.

DESPITE technical advances in the surgical and radiotherapeutic management of carcinoma of the oropharynx, successful treatment remains a difficult problem. Local control continues to be an elusive goal, not only for patients with advanced tumors but also for those with earlier stage carcinomas. To enlarge upon our present knowledge of the natural history of this disease, and to establish guidelines for a proposed trial of combined surgery, radiation therapy, and chemotherapy, a review of all patients treated initially with radiation therapy for squamous cell carcinoma of the oropharynx at the Stanford University Medical Center Division of Radiation Therapy was undertaken.

MATERIAL AND METHOD

Between 1956 and 1973, 305 patients with squamous cell carcinomas of the oropharynx underwent radiation therapy

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with curative intent at the Stanford University Medical Center, utilizing megavoltage external beam radiation therapy (4.8 MeV Stanford Medical Linear accelerator, 6 MeV and 4 MeV LINAC accelerators).[9] Follow-up intervals ranged from a minimum of two years to a maximum of 16 years. Treatment techniques varied with both the location of the primary site and local tumor extent, as well as the presence or absence of clinically involved lymph nodes and are listed when individual oropharyngeal sites of involvement are discussed. All patients were staged by the TNM system according to the 1962 UICC Classification outlined in Table I. This classification divides the oropharynx into several sites, consisting of the anterior wall (valleculae and base tongue), lateral wall (tonsils and faucial pillars), superior wall (soft palate and uvula), and posterior aspect (posterior oropharyngeal wall). This analysis of the results of treatment at Stanford is organized in accordance with these anatomic subdivisions. Excluded from consideration were: three patients with a pathologic diagnosis other than squamous cell carcinoma; 64 patients referred for consultation only; twelve treated with palliative intent; eleven patients treated with radiation therapy at other institutions prior to referral; one patient who refused therapy; and another who died soon after the initiation of radiation therapy.

From January, 1968, through December, 1972, a randomized protocol for the treatment of advanced squamous cell carcinoma of the upper respiratory tract was in effect. Surgery alone, radiation therapy alone or a combination of surgery and radiation therapy were compared. These results are analyzed separately. However, patients from this protocol who had oropharyngeal lesions are included in this analysis in reference to sites of their lesion.

Table I

OROPHARYNX CARCINOMA: TNM STAGING (UICC 1962)

T_1—Tumor limited to one site
T_2—Tumor extending beyond one site, limited to oropharynx
T_3—Tumor extending beyond oropharynx
N_1—Clinically involved ipsilateral lymph node(s)
N_2—Clinically involved contralateral or bilateral lymph nodes
N_3—Fixed lymph node(s)

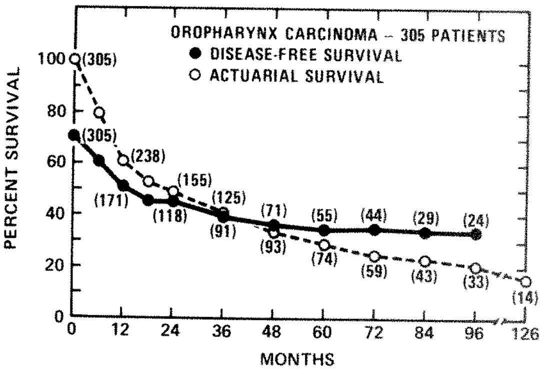

Fig. 1. Actuarial and disease-free survival for all 305 patients with oropharyngeal carcinomas. The curve for actuarial survival is altered by any death, whether from primary site or neck failure, distant metastases, intercurrent diseases, or second primary malignancies. The curve for disease-free survival decreases only when a local or distant relapse occurs, and does not begin at 100 percent because certain patients were never free of their oropharyngeal cancer.

RESULTS

ALL OROPHARYNX SITES

Actuarial (Berkson-Gage)[4] and disease-free survival curves were calculated from the completion of radiation therapy for all patients with oropharyngeal carcinoma (Fig. 1). Thirty-five percent actuarial and 37 percent disease-free five year survivals were noted. Actuarial survival includes deaths not only from the primary carcinoma, but also from intercurrent disease and secondary primary malignancies. The curve for disease-free survival is decreased only when a relapse occurs.

Distant metastases occurred in 52 (17 percent) of the 305 patients, as shown by Table II. The most common metastatic sites were lung, liver, and bone. Distant metastases occurred in 18 (13.4 percent) of the subgroup of 134 patients in whom con-

Table II

OROPHARYNX CARCINOMA: DISTANT METASTASES: 52 of 306 PATIENTS (17 PERCENT)

Lung	35
Liver	17
Bone	13
Brain	5
Mediastinum	8
Kidney	5
Spleen	4
Other sites (peritoneum, pleura, pericardium, adrenals, skin, heart)	21

trol of the primary lesions and cervical lymph nodes was obtained. Almost 25 percent of patients with base of the tongue carcinomas whose primary sites remained controlled ultimately developed distant metastases. Table III demonstrates the frequent incidence of second primary malignancies in oropharyngeal cancer. Additional neoplasms developed in 49 of 305 patients, an incidence of 16 percent. The majority involved the upper respiratory tract and lungs.

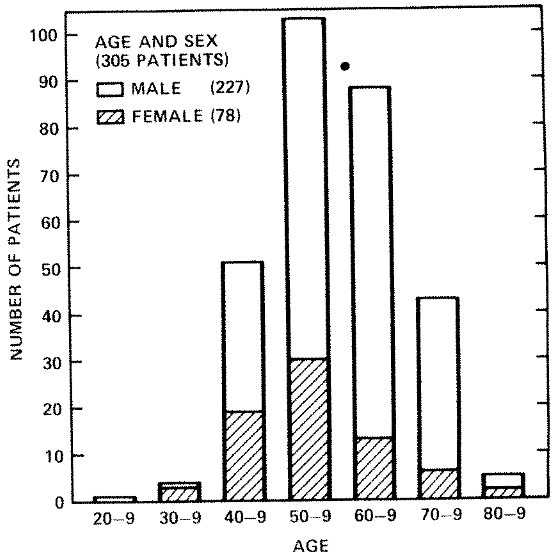

Fig. 2. Age, sex distribution for all patients with oropharyngeal carcinomas.

Table III

OROPHARYNX CARCINOMA: SECOND PRIMARY NEOPLASMS: 49 of 306 PATIENTS (16 PERCENT)

Head and neck (oral tongue, tonsil, soft palate, floor of mouth, alveolar ridge, hypopharynx, larynx)	26
Lung	8
Esophagus	6
Leukemia*	3
Lip	2
Pancreas	1
Colon	2
Hepatoma	2
Prostate	2
Stomach	1
Melanoma	1
Adenocarcinoma (primary unknown)	1

* Acute lymphocytic leukemia (1); chronic lymphatic leukemia (2).

Figure 2 tabulates the sex and age distribution by decade for all patients. The male to female preponderance was almost three to one (227:78).

Control of initially involved cervical lymph nodes, using radiation therapy alone, was achieved in 56 percent of the patients (Table IV). Failure to control nodal metastases was usually accompanied by failure at the primary site. In addition, surgical salvage of radiation therapy failures in the neck region was seldom successful for the same reason.

Subsequent lymph node metastases in patients with initially uninvolved necks were rare (16 percent) if the radiation therapy fields included at least the primary

Table IV

OROPHARYNX CARCINOMA: CONTROL OF INITIALLY INVOLVED REGIONAL LYMPH NODES WITH RADIATION THERAPY

	Nodal Control: Radiation Therapy Alone	Primary Uncontrolled with Neck Uncontrolled
T_X N_1	60/91 (67 percent)	27/31
T_X N_2	12/25 (48 percent)	12/13
T_X N_3	34/74 (46 percent)	37/40

site and regional lymph nodes. Most of these late neck failures occurred in patients with uncontrolled primary sites (Table v). If supplemental neck fields were used, 77 of 83 patients (92 percent) remained free of cervical lymph node metastases.

Table V

OROPHARYNX CARCINOMA: CONTROL OF INITIALLY UNINVOLVED REGIONAL LYMPH NODES (T_XN_0) WITH RADIATION THERAPY

	Radiation Therapy: Primary and Necks	Radiation Therapy: Primary only
Nodal control	77/83 (92 percent)	28/33 (84 percent)
Lymph nodes uncontrolled	6*	5*

* 8/11 Patients: primary failure and neck failure.

TONSIL

One hundred and forty patients with tonsillar cancers were irradiated. Radiation doses were usually 6,600 rads in six to six and one-half weeks, with four or five fractions per week. This dose was occasionally exceeded with large, slowly regressing neoplasms. Therapy techniques consisted of opposed lateral fields with equal or unequal weighting in 108 cases, right angle wedged intersecting fields in 20 patients, and angled ipsilateral wedged fields in twelve instances. Cervical lymph nodes were treated by anteroposterior opposed fields with midline spinal cord shielding before 1967. However, direct anterior fields alone with a midline bar were used after 1968, with radiation doses of 5,000 rads in five weeks at 3 cm depth for uninvolved necks. This modification of our technique of neck irradiation was made to avoid an excessive incidence of severe neck fibrosis associated with the earlier anteroposterior technique.

TNM Stage; Local Control and Primary Site: Table vi lists both the initial stages and local control rates for all patients by TNM staging. There were both a large number of T_3 lesions (70/140) and a high incidence of regional lymph node metastases at presentation (60 percent). Local control of the primary site was achieved in 71 percent of T_{0-1} lesions, 62 percent of T_2 lesions, and 33 percent of T_3 lesions, with a minimum follow-up period of two years.

Lymph Nodes: Control of clinically involved cervical lymph nodes is tabulated in Table vii, again reflecting the decreased radiocurability of squamous cell cancer with increasing tumor size. The eradication of nodal metastases diminished from 65 percent in those with N_1 lymphadenopathy to 31 percent in patients with N_3 involvement. Failure to eliminate lymph node metastases was accompanied by failure to control the primary site in most instances (13/16—N_1, 17/20 with N_3 cervical lymphadenopathy).

The statement that prophylactic radical

Table VI*

TONSIL CARCINOMA: LOCAL CONTROL OF PRIMARY TUMOR

	N_0	N_1	N_2	N_3	Total
T_0	2/2				2/2 (71 percent)
T_1	6/8	3/6		1/1	10/15
T_2	22/28	9/18	1/2	1/5	33/53 (62 percent)
T_3	11/22	7/22	2/3	4/23	24/70 (34 percent)
Total	41/60	19/46	3/5	6/29	69/140 (50 percent)

* Initial TNM staging and local control rates for patients with tonsil carcinomas (minimum 2 year follow-up period).

TABLE VII

TONSIL CARCINOMA: CONTROL OF INITIALLY INVOLVED REGIONAL LYMPH NODES WITH RADIATION THERAPY

	Nodal Control: Radiation Therapy Alone	Primary Uncontrolled with Neck Uncontrolled
T_x N_1	30/46 (65 percent)	13/16
T_x N_2	4/5 (80 percent)	1/1
T_x N_3	9/29 (31 percent)	17/20

neck dissection is indicated for patients with tonsil carcinoma[11,12] is not substantiated by our data. Most patients whose cervical lymph nodes were treated electively with radiation therapy failed to develop subsequent nodal metastases (41/43 = 95 percent). However, radiation therapy to the primary site only, which also included the regional lymph nodes, was also effective in preventing late cervical lymph node metastases in most patients (Table VIII).

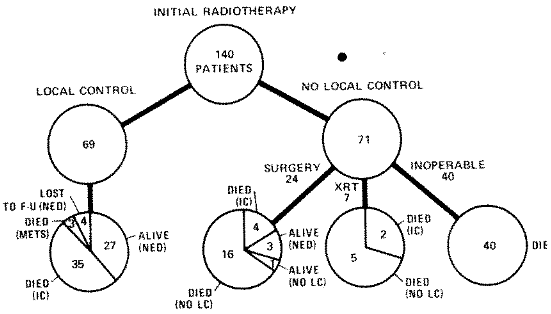

FIG. 3. Local control, 140 patients with tonsillar carcinomas. Local control was obtained by radiation therapy alone in 69/140 patients (49 percent). Approximately one-third of the patients whose primary cancers were not controlled by radiation therapy were operable (24/71), but only eight of these patients were controlled locally by the additional surgery.

Complications: The most common complication was mandibular osteoradionecrosis in 18 of the 140 patients (13 percent). There were no significant differences in incidence of osteoradionecrosis when treatment by right angle wedged fields, opposed lateral portals or angled oblique wedged fields were compared. This was successfully managed by conservative alveolectomy or debridement in 14 instances. Other complications were persistent mucosal ulceration in five patients and miscellaneous postirradiation sequelae in eight others, including hypoglossal nerve paralysis and pharyngeal necrosis, each in single patients, and postoperative hemorrhage from the carotid artery in two others.

Follow-Up Status; Surgical Salvage: The status at last follow-up is shown in Figure 3. Local control was achieved in one-half of the patients. Approximately ten percent of the primary site failures were salvaged by a variety of surgical procedures. Disease-free and actuarial survival for carcinoma of the tonsil are shown in Figures 4 and 5. Lower five year results for actuarial than disease-free survival for patients with T_1 and T_2 primary lesions reflect deaths from

TABLE VIII

TONSIL CARCINOMA: CONTROL OF INITIALLY UNINVOLVED REGIONAL LYMPH NODES

	Radiation Therapy: Primary and Necks	Radiation Therapy: Primary only
Nodal control	41/43 (95 percent)	15/17 (88 percent)
Lymph nodes uncontrolled	2*	2*

* 3/4 Patients: primary failure with neck failure.

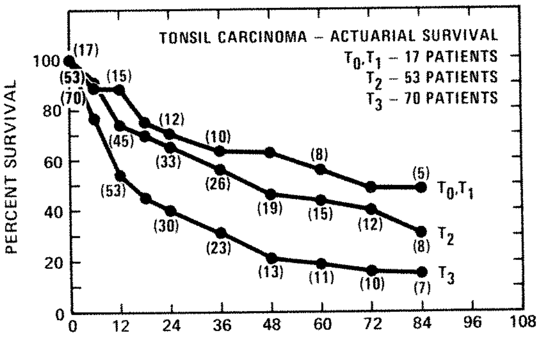

FIG. 4. Actuarial survival curve for carcinoma of the tonsil.

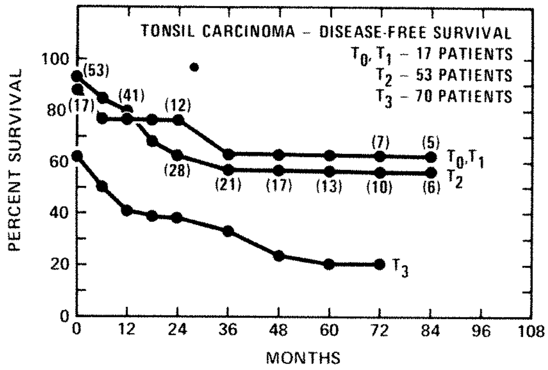

FIG. 5. Disease-free survival in carcinoma of the tonsil.

intercurrent diseases and second primary neoplasms.

BASE OF THE TONGUE

One hundred and four patients received radiation therapy for squamous cell carcinoma of the base of the tongue, or valleculae or both. The technique used for primary tumor treatment was opposed lateral fields which included the oropharynx, superior hypopharynx, and primary echelon lymph nodes (jugulodigastric, juguloparotid, jugulocarotid, and submaxillary). Tumor doses for primary sites, clinically involved cervical lymph nodes, and elective neck irradiation were identical to those used for patients with tonsillar carcinomas.

TABLE X

BASE OF THE TONGUE CARCINOMA: LOCAL CONTROL: CLINICALLY INVOLVED CERVICAL LYMPH NODES

Stage	Radiation Therapy Alone	Total (Includes Salvage of Radiation Therapy Failures)
T_X N_1	17/29 (59 percent)	18/29 (62 percent)
N_2	5/15 (33 percent)	6/15 (40 percent)
N_3	17/32 (53 percent)	20/32 (62 percent)

TNM Stage; Local Control of Primary Site: Table IX shows the initial TNM stages for all patients with base of the tongue carcinoma. Local control of the primary site was obtained in 44 percent of the patients (46/104). However, surgical salvage attempts were possible in only 25 percent of those patients who failed locally.

Lymph Nodes: The results of irradiating clinically involved cervical lymph nodes are shown in Table X. Twenty-three of 28 patients (82 percent) whose cervical lymph nodes were electively irradiated remained free of nodal metastases. Since persistent primary cancers were present in four of five patients with uncontrolled cervical lymph nodes, it is likely that reseeding of the cervical lymph nodes could have accounted for most of these late neck failures (Table XI).

Complications: Postradiation therapy complications, as do those in tonsillar and palatine carcinomas, reflect an aggressive approach to oropharyngeal malignancy. However, the previously described alteration in treatment techniques for neck

TABLE IX*

BASE OF THE TONGUE CARCINOMA: LOCAL CONTROL: PRIMARY

	N_0	N_1	N_2	N_3	Total
T_1	1/3	5/11	1/1	1/4	8/19
T_2	10/13	3/7	3/6	5/9	21/35
T_3	4/12	2/12	3/8	8/18	17/50
Total	15/28	10/30	7/15	14/31	46/104

* Local control rate, initial TNM stages, for patients with base of tongue carcinomas (minimum 2 year follow-up period).

TABLE XI

BASE OF THE TONGUE CARCINOMA: CONTROL OF CLINICALLY UNINVOLVED CERVICAL LYMPH NODES (T_X N_0)

	Radiation Therapy to Primary Site only (7 pt.)	Radiation Therapy to Primary Site and Neck(s)—(21 pt.)
Lymph nodes controlled (remained N_0)	6 (86 percent)	17 (81 percent)
Neck failure	1*	4*

* 4 of 5 neck lymph node failures occurred in patients with uncontrolled primaries.

TABLE XII*

BASE OF THE TONGUE CARCINOMA: COMPLICATIONS OF RADIATION THERAPY: 24 OF 104 PATIENTS (23 PERCENT)

Complication	No. of Patients	Radiation Therapy Dose	Fields	Treatment	Comment
Mandibular osteoradionecrosis	6	6,575 rads/51 days	Lateral	Excision	Healed
		6,600 rads/50 days	Lateral	Conservative	Healed
		6,400 rads/54 days	Lateral	Post dental extraction	Fistula
		6,600 rads/43 days	Lateral	Post dental extraction	Healed
		6,525 rads/44 days	Lateral	Excision	Healed
		6,850 rads/47 days	Lateral	Conservative	Healed
Severe neck fibrosis	8	6,600 rads/43 days	Anteroposterior		Cranial nerve dysfunction
		6,600 rads/46 days	Anteroposterior		Brachial plexus pain
		6,600 rads/47 days	Anteroposterior		
		5,900 rads/56 days	Anteroposterior		Necks boardlike
		6,800 rads/45 days	Left anterior		
		6,500 rads/42 days	Anteroposterior		
		7,150 rads/49 days	Anteroposterior		
		7,150 rads/51 days	Anteroposterior		
Severe mucositis and/or edema	4	6,700 rads/41 days	Lateral		
		6,600 rads/40 days	Lateral		
		6,000 rads/45 days	Lateral		
		6,500 rads/51 days	Lateral		
Others	7				
C5-6 osteomyelitis	1	8,000 rads/81 days	Lateral		Hydrea treatment—lethal
Cerebral vascular accident, external carotid catheterization	1				Permanent
Dehydration and hospitalization post radiation therapy	1	6,950 rads/53 days	Lateral		NED
Epiglottic ulcer, tracheitis, hemorrhage	1	7,100 rads/48 days	Lateral		Healed
Bilateral hypoglossal paralysis	1	8,000 rads/73 days	Lateral		NED
Laryngeal chondritis, tracheostomy	1	7,200 rads/41 days	Lateral		NED
Necrosis, cricoid cartilage	1	6,600 rads/45 days	Lateral		Laryngo-cutaneous fistula, NED

* Post-irradiation complications, 104 patients with base of the tongue carcinomas. Severe neck fibrosis is no longer seen following the use of anterior radiation portals only for supplemental neck fields (see text). NED= no evidence of disease.

lymph nodes has resulted in a decreased frequency of severe, late cervical fibrosis (Table XII).

Survival: The status at last follow-up is seen in Figure 6, showing initial control of the primary lesion by radiation therapy alone in 43 of 104 patients (42 percent). Local control was obtained in another ten

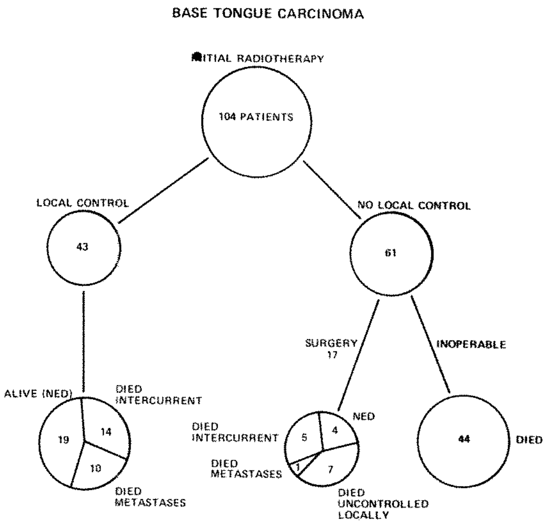

FIG. 6. Local control, 104 patients with base of the tongue carcinomas, minimum two year follow-up interval. Note that almost 25 percent of those patients with local control by radiation therapy alone died with distant metastases (10 of 43).

patients by surgical salvage of irradiation failures. Figures 7 and 8 show disease-free and actuarial survival. Patients with T_1 and T_2 primary lesions had almost identical relapse-free survival curves, both higher than that for patients with T_3 lesions.

PALATE AND UVULA

Initial Stage; Local Control; Complications: Thirty patients received external beam radiation therapy as primary treatment of squamous cell carcinoma of the soft palate and uvula. Treatment techniques and tumor doses were both similar to those used for base of the tongue carcinomas. The primary sites were controlled in 50 percent of the patients (Fig. 9). The most frequent complication was mandibular osteoradionecrosis, which occurred in four of these 30 patients (14 percent). Two of these patients ultimately required hemimandibulectomy for control of the osteoradionecrosis.

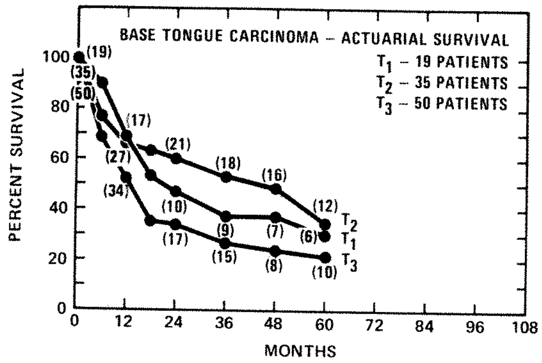

FIG. 7. Actuarial survival curve for carcinoma of the base of the tongue.

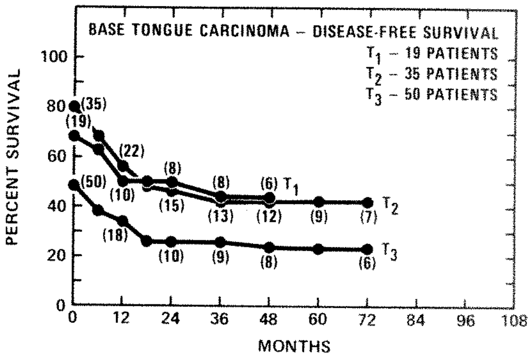

Fig. 8. Disease-free survival in carcinoma of the base of the tongue.

Follow-Up Status: The status at last follow-up is seen in Figure 9. Disease-free and actuarial survival are depicted in Figure 10, showing identical five year values of 38 percent.

POSTERIOR AND LATERAL OROPHARYNGEAL WALLS

Thirty-one patients were irradiated for squamous cell carcinomas arising in the posterior and lateral oropharynx. Treatment techniques and tumor doses were

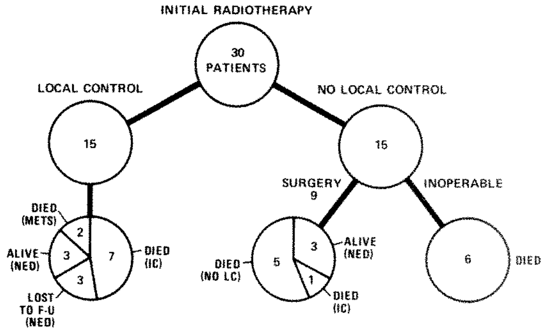

FIG. 9. Local control, 30 patients with cancer of the palate and uvula treated initially by radiation therapy alone.

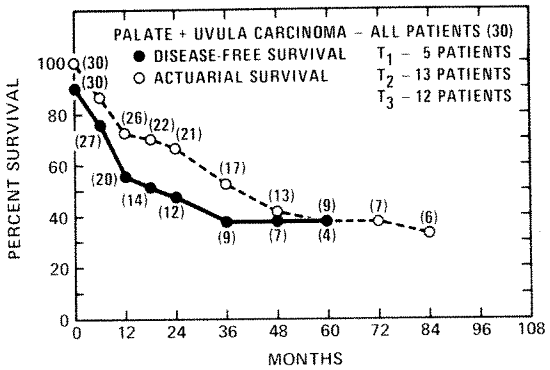

Fig. 10. Survival curves for carcinoma of the palate and uvula.

similar to those employed for the other oropharyngeal sites.

TNM Staging; Primary Site, Results: Most patients not only had T_3 primary lesions (81 percent) but also a high incidence of palpable cervical lymph node metastases (61 percent). Control of the primary lesion was achieved in twelve of 31 patients (39 percent) (Fig. 11). Three year disease-free and actuarial survival for this small number of patients were both less than 25 percent.

Complications; Follow-Up Status: A postradiation therapy complication occurred in only one patient (mandibular osteoradionecrosis). The status at last follow-up is depicted in Figure 11.

ADVANCED HEAD AND NECK PROTOCOL

Twenty-two patients were entered into a controlled clinical trial between 1969 and 1972, which compared surgery alone, radiation therapy alone, and the two modalities combined for extensive, advanced carcinomas of the hypopharynx, oropharynx, and supraglottic larynx (Fig. 12). The TNM staging and anatomic sites of involvement are listed in Table XIII.

Patients who were initially operable were randomized between surgery or full-dose radiation therapy alone, or preoperative irradiation (5,500 rads in five and one-half weeks). Fourteen patients were found to be operable at presentation. All four who were treated initially by surgery alone failed at the primary site. Five patients received radiation therapy alone; four had persistent primary neoplasms postirradiation, but the other is alive without evidence of disease. Preoperative radiation therapy was given to five patients, two of whom died with persistent primary cancers. The other three patients were controlled locally; one is alive without evidence of disease, one died without evidence of disease, and the third died with distant metastases.

If initially inoperable (eight patients), the primary site and neck received 5,500 rads in standard fractionation. These patients were subsequently randomized between surgery or additional radiation therapy if their primary lesions became operable after the initial course of irradiation. If still inoperable, radiation therapy was continued. Two patients who became operable were randomized to surgical treatment and died subsequently free of disease. Two others were randomized to continue their radiation therapy course; one is alive without evidence of disease, but the other died with persistent primary cancer. The four who remained inoperable all died with uncontrolled carcinoma at the primary site.

DISCUSSION

This detailed analysis of a large group of patients was made possible because treatment was carried out in a consistent fash-

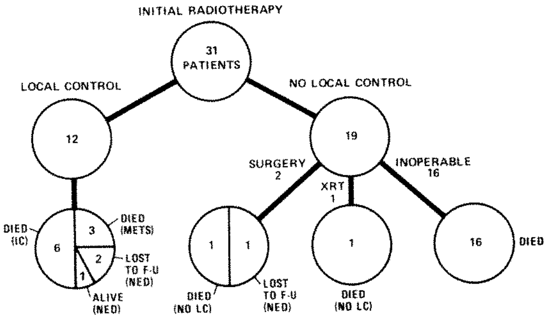

Fig. 11. Local control, 31 patients with involvement of the posterior and lateral oropharyngeal walls. Local control obtained in twelve of 31 patients (29 percent) despite many advanced primary lesions: T_1—four patients, T_2—two patients, and T_3—25 patients.

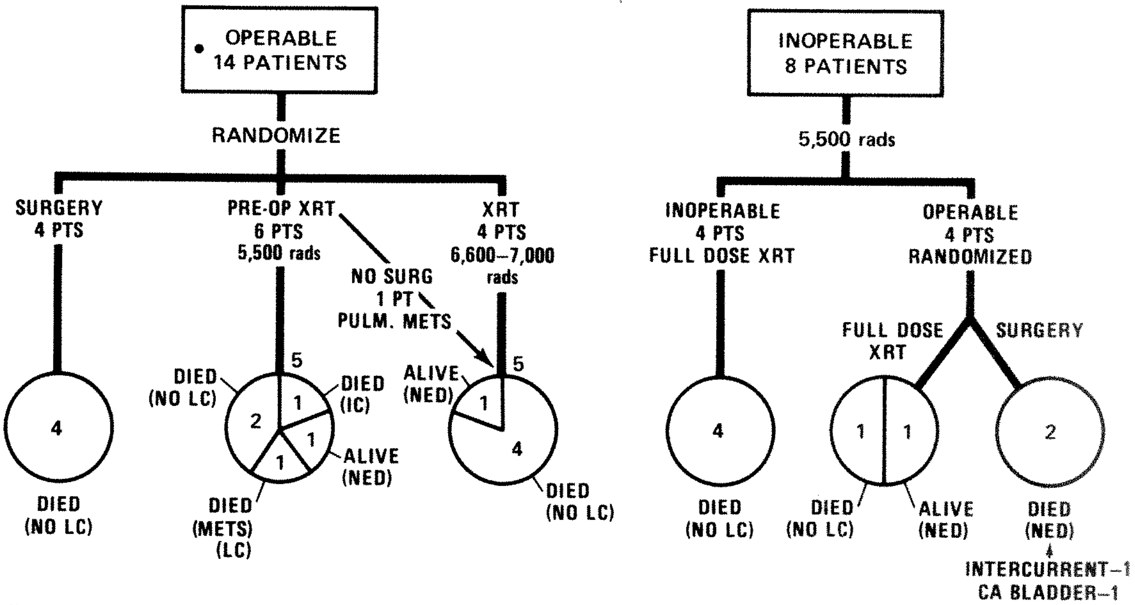

FIG. 12. Results in patients with advanced, extensive carcinomas of the hypopharynx, oropharynx, and supraglottic larynx randomized between surgery, radiation therapy alone or the two modalities combined. (See text.)

ion, utilizing megavoltage external beam radiation therapy exclusively. In addition, follow-up examinations were performed in a combined clinic staffed by radiotherapists and ear, nose, and throat surgeons.

A high incidence of additional primary malignancies, and a large proportion of deaths due to intercurrent disease inherently limit the survival rate in this patient group. In this regard, we believe that determination of both actuarial and disease-free survival is valuable to better characterize the patient group and therapeutic results.

A high percentage of clinically involved cervical lymph nodes was controlled by radiation therapy alone (67 percent—N_1, 48 percent—N_2 and 46 percent—N_3). However, failure of radiation therapy to control cervical lymph node metastases also correlated with persistent primary cancer since of 86 neck lymph node radiation therapy failures, only eight occurred in patients with controlled primaries.

The expected high incidence of late nodal metastases was also decreased by prophylactic irradiation of cervical lymph nodes. Failure to control the primary neoplasm usually coincided with subsequent lymph node metastases, a finding consistent with previous reviews of radiation therapy results in the head and neck region.[7] Therefore, if the primary cancer is eradicated, subclinical lymph node metastases may then be controlled with radiation therapy.[3,10] Radiation therapy for prophylaxis of clinically negative necks is advocated in place of elective radical neck dissection, based on the frequent occurrence of nodal metastases in the untreated neck in patients with oropharyngeal carcinoma and the ability of radiation therapy to eliminate suspected subclinical nodal disease, as seen in Tables V, VIII; and XI.[8]

Although the primary tumor can be controlled by radiation therapy in many instances, we found a high percentage of local failures in patients with T_3 lesions (75 percent). These results suggest that additional modalities of therapy are needed to improve primary tumor control, particularly in advanced stages. A high incidence of radiation therapy complications also suggests the need to reduce the volume of ir-

TABLE XIII*

HEAD AND NECK PROTOCOL—22 PATIENTS—TNM STAGING

Randomization	Sex	TNM Stage	Site
Radiation therapy alone:	M	$T_1\ N_0$	Pyriform sinus
	M	$T_1\ N_2$	Pyriform sinus
	M	$T_3\ N_1$	Pyriform sinus
	M	$T_3\ N_1$	Pyriform sinus
	M	$T_4\ N_2$	Epiglottis (randomized preoperative, metastases discovered during radiation therapy—no surgery
Preoperative radiation therapy:	M	$T_3\ N_1$	Pyriform sinus
	F	$T_3\ N_1$	Pyriform sinus
	M	$T_3\ N_3$	Pyriform sinus
	M	$T_4\ N_0$	Epiglottis
	F	$T_4\ N_1$	Epiglottis
Surgery only:	M	$T_1\ N_0$	Posterior pharyngeal wall
	M	$T_3\ N_0$	Pyriform sinus
	M	$T_3\ N_1$	Pyriform sinus
	F	$T_3\ N_2$	Base of the tongue
Inoperable throughout—radiation therapy only:	M	$T_3\ N_3$	Pyriform sinus
	M	$T_3\ N_3$	Pyriform sinus
	M	$T_3\ N_3$	Pyriform sinus
	M	$T_3\ N_3$	Pyriform sinus
Became operable after 5,500; randomized to radiation therapy:	M	$T_1\ N_3$	Pyriform sinus
	M	$T_3\ N_0$	Posterior cricoid
Became operable after 5,500; randomized to surgery:	M	$T_3\ N_0$	Pyriform sinus
	M	$T_3\ N_3$	Pyriform sinus

* TNM staging, 22 patients entered into Advanced Head and Neck Protocol comparing radiation therapy and surgery alone and in combination. Note unfavorable lesions, most of which involve hypopharyngeal primary sites.

radiated tissue, but at the same time giving a higher dose to the primary site in accessible lesions, possibly by increased use of interstitial techniques. Combining preoperative irradiation and surgery for late-stage oropharyngeal carcinoma gave improved local control, although survival was poor because of distant metastases. Surgery alone is probably not ideal management for patients with extensive lesions since all of the patients treated this way in our randomized study failed locally.

The frequency of distant metastases, especially for patients with carcinoma of the base of the tongue, cannot be reduced by local modalities such as radiation therapy or surgery and this suggests a need for adjuvant chemotherapeutic approaches. However, the single agents presently available do not have a high degree of success in controlling squamous cell carcinomas.[5] Our present plans include multiagent chemotherapy, surgery, and radiation therapy for most patients presenting with T_2 and T_3 oropharyngeal squamous cell carcinoma in a controlled clinical trial.

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FEBRUARY, 1976

NON-RANDOMIZED COMPARISON OF PREOPERATIVE IRRADIATION AND SURGERY *versus* IRRADIATION ALONE IN THE MANAGEMENT OF CARCINOMA OF THE TONSIL*

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ABSTRACT:

This is a non-randomized comparison of 98 patients with epidermoid carcinoma of the tonsil treated by preoperative irradiation and surgery and 97 patients receiving irradiation alone. Patients treated with preoperative irradiation received, in most instances, 3,000 rads tumor dose in three weeks through ipsilateral portals, followed within two to six weeks after completion of therapy by an *en bloc* tumor resection and radical neck dissection. The group treated with irradiation alone received tumor doses in the range of 5,500–6,500 rads in six weeks. No significant difference was noted in the survival yielded by either treatment modality. Both treatment modalities were equally effective in controlling the tumor in the metastatic ipsilateral lymph nodes. In selected cases, a combination of both modalities may offer better results, but this remains to be proved.

EXCELLENT reports have been published on the effectiveness of radiation therapy alone in the treatment of epithelial tumors of the tonsil.[8,13,14,16,17,19,21] Because of the seemingly high incidence of local or neck lymph node failures after irradiation in some institutions and the comparatively poor survival rates with surgical procedures, a combined approach has gained popularity in the past ten years.[4,12,18] This retrospective study compares the results, sites of failure, complications, and mortality of irradiation alone or combined with a surgical procedure in the management of patients with carcinoma of the tonsil. There are some shortcomings, such as the extended period of time and different techniques used in the radiation therapy of these patients and the lack of criteria for selection of either treatment modality. This is an updated analysis from previous reports with additional patients and longer follow-up.[13,14]

MATERIAL AND METHOD

All the clinical records of patients with proved carcinoma of the tonsil receiving primary treatment in the Division of Radiation Oncology and Barnes Hospital, Washington University Medical Center were reviewed, as well as a few patients irradiated by us and operated upon by the Staff of the Department of Otolaryngology at City Hospital and the Veterans Administration Hospital between January, 1954 and June, 1972. During this period of time, a total of 98 patients was treated by preoperative irradiation and surgery, and 97 by irradiation alone. The pathologic slides of the initial biopsy and the operative specimens, when available, and the pathology reports of all patients, were reviewed

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From the Clinical Section, Division of Radiation Oncology, Mallinckrodt Institute of Radiology, and the Division of Surgical Pathology, and the Department of Otolaryngology, Washington University School of Medicine, St. Louis, Missouri.

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by two of the authors (L.V.A. and C.A.P.). All patients except two have been followed, either at this institution or by correspondence with the local physicians, or in some cases, relatives. The two patients lost to follow-up were tabulated as dead with tumor. If the patients had no clinical evidence of tumor at the time of death, they were considered as dying from intercurrent disease.

The patients were staged in retrospect using the description from the charts and the diagram of the primary tumor and the metastatic neck lymph nodes. The following system was used:

Primary Tumor

- T_1—Lesions localized to the tonsil, less than 3 cm in diameter
- T_2—Lesions 3–5 cm in diameter, with limited extension to adjacent structures
- T_3—Lesions larger than 5 cm, without extensive involvement of adjacent structures
- T_4—Massive tumors extending from the nasopharynx down to the base of the tongue, epiglottis or lateral pharyngeal wall.

Metastatic Lymph Nodes in the Neck

- N_0—No clinical lymph node involvement
- N_1—Single, less than 3 cm in diameter, mobile lymph node
- N_2—Single, mobile lymph node larger than 3 cm or multiple ipsilateral non-fixed lymph nodes
- N_3—Large fixed, unilateral lymph node or bilateral lymphadenopathy.

Figure 1 shows the distribution of patients according to the clinical stages. It is evident that 75 percent of the patients in the preoperative group were in early stages $(T_{1,2,3}\text{–}N_{1,2})$, in contrast to only 50 percent of the patients in the irradiation alone group.

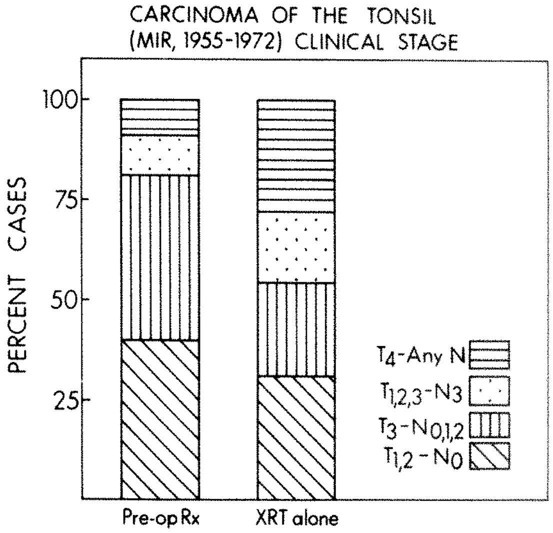

Fig. 1. Distribution according to clinical staging of 98 patients with carcinoma of the tonsil treated with preoperative irradiation and surgery, and 97 patients receiving irradiation alone. (W. U. Neg. 75-4350.)

The age distribution is shown in Figure 2 and is comparable for both groups. There were a few more women in the irradiation alone group (24 percent) as opposed to the preoperative irradiation group (15 percent).

The exact location of the recurrences following treatment was determined as accurately as possible. In the radiation therapy group, it was assumed that if there was a failure in the oropharynx, it was in the tonsillar fossa, unless specifically indicated. In the preoperative group, it was presumed that the operation removed the

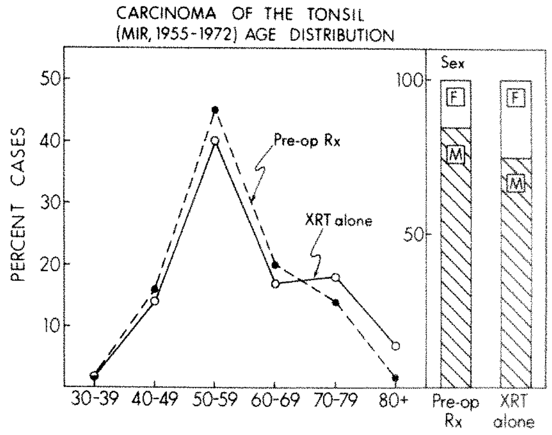

Fig. 2. Age and sex distribution, comparable in both groups. (W. U. Neg. 75-4349.)

gross bulk of disease in the tonsil and therefore, any failures in the oropharynx were considered marginal (except in a few patients who were not operated upon following preoperative irradiation).

If information was not recorded concerning metastatic lymph nodes in the neck, these were presumed to be ipsilateral, unless otherwise specified.

TREATMENT METHODS

Details of treatment portals and dose distributions were reported previously.[14]

Preoperative Irradiation: Ninety-eight patients received varying doses of preoperative irradiation, usually 2,000–3,000 rads tumor dose in two to three weeks to the primary tumor and the ipsilateral neck lymph nodes through an oblique appositional portal with Cobalt 60 or 4 MeV x rays. Two to four weeks after completion of radiation therapy, a radical tonsillectomy combined with a jaw-neck dissection was performed in the majority of the patients. Two patients with small lesions (T_1, N_0) were treated with wide resections of the primary tumor without neck dissection. Included in this group were two patients who refused surgery and received irradiation alone, three patients who died during or after the irradiation before the operation was carried out, and three patients who were judged to be inoperable after their planned preoperative irradiation, because of slow regression of extensive oropharyngeal tumors or large neck lymph nodes.

Ninety-seven patients were treated by radiation therapy alone. Prior to 1959, parallel opposing lateral portals were used to deliver to doses in the range of 5,000 rads in six weeks to 6,000 rads in seven weeks using 250 KV x rays. Between 1960 and 1970, patients were treated to doses of 6,000–6,500 rads to the primary tumor and the upper neck, and 5,000–6,000 rads tumor dose at 3 cm to the lower neck, depending on whether or not they had palpable neck lymph nodes. After 1970, patients with more extensive lesions (T_3–T_4) received approximately 7,000 rads tumor dose to the primary and involved lymph nodes and 6,000 rads to prophylactically treated areas. The daily tumor dose was 180–200 rads, five fractions per week.

A surgical procedure was performed in 17 of these patients because of suspected or proved primary tumor or neck lymph node persistence or recurrence. This group of patients is considered as treated by irradiation alone in the survival computations.

PATHOLOGICAL FINDINGS

All patients were diagnosed as having epithelial tumors. A histological classification of tumors of the tonsil was proposed in a previous publication:[14]

A. Epidermoid carcinoma
   1. Keratinizing
   2. Non-keratinizing

   These were separated into well-differentiated, intermediate or poorly-differentiated.
   3. Non-specified (includes all the patients on whom the initial pathological diagnosis was epidermoid carcinoma but the slides were not available for review)

B. Undifferentiated carcinoma

C. Lymphoepithelioma

Pathologically, the majority of the cases studied represent squamous cell carcinoma and its variants. Most of the cases have slightly keratinizing squamous cell carcinoma with a plexiform pattern. In a few instances, there is extremely prominent keratinization. The so-called lymphoepithelioma is very rare in this location.

The patients receiving preoperative irradiation had certain common pathologic findings, the operation usually being done three to five weeks after the completion of radiation therapy. In practically all instances, the overlying epithelium had reepithelialized and often beneath this epithelium, extremely prominent fibrosis was present, particularly in the areas where tumor had existed (Fig. 3). Within these fibrotic zones, it was not unusual to find remnants of dead tumor often surrounded by giant cells (Fig. 4). Some of the small vessels were thrombosed, but foam cell changes were infrequent. The accessory salivary gland tissue almost invariably showed radiation effect. The acinar tissue was first affected but with profound changes, resulting in almost complete obliteration of acini with only remnants of ducts. It was remarkable that with the moderate doses employed, prominent muscle destruction was present with focal areas of fibrosis. A study of the lymph nodes demonstrated that they had repopulated for the most part, developing good germinal centers (Fig. 5), and in some instances, there was striking histiocytic proliferation (Fig. 6). This histiocytic reaction was, at times, present also in the salivary gland tissue. Some lymph nodes, obviously involved clinically, showed partial fibrotic replacement and masses of keratin but no microscopic evidence of tumor (Fig. 7). In approximately 40 percent of the specimens, viable carcinoma was identified in the tonsil or the lymph nodes (Fig. 8, *A* and *B*).

RESULTS

Absolute Survival After Treatment: Table I shows the absolute three year survival rates without evidence of tumor recurrence. No difference was noted in the survival, within comparable stages, when the patients were treated by either preoperative irradiation and surgery or irradiation alone.

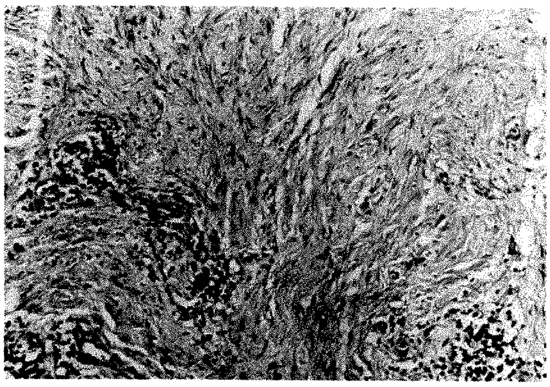

Fig. 3. Extensive postirradiation fibrosis with no tumor. (V. A. Neg. 3100G.)

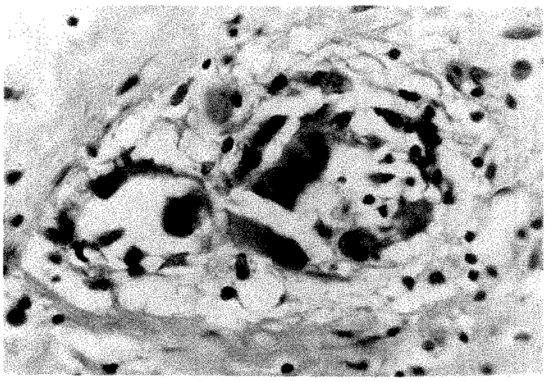

Fig. 4. This is the only evidence of remaining cancer. Clusters of foreign body giant cells surrounding remnants of keratin. (V. A. Neg. 3100C.)

Histological Characteristics and Survival (Table II): Approximately 60 percent of the patients had keratinizing epidermoid carcinoma. The greatest proportion was moderately differentiated. Although the groups of patients were small, there was no significant difference in the survival between the keratinizing and non-keratinizing varieties of epidermoid carcinoma, and the degree of differentiation of the tumor did not affect the prognosis. Patients initially diagnosed as having epidermoid carcinoma and on whom the slides were not available for review were classified as epidermoid carcinoma, unspecified. Their survival is approximately the same as in other groups. Three patients with early lymphoepithelioma (T_1, T_2) were surviving at three years without evidence of recurrence.

Findings in Postirradiation Pathological Specimens and Correlation with Prognosis (Table III): The absence of viable tumor in the tonsil or in the lymph nodes was associated with an excellent prognosis, regardless of the initial stage of the disease. Approximately 90 percent of the patients in this category survived over three years without evidence of tumor. If the primary tumor or the lymph nodes contained viable carcinoma, the survival rate was approximately 40 percent (seven out of 18 pa-

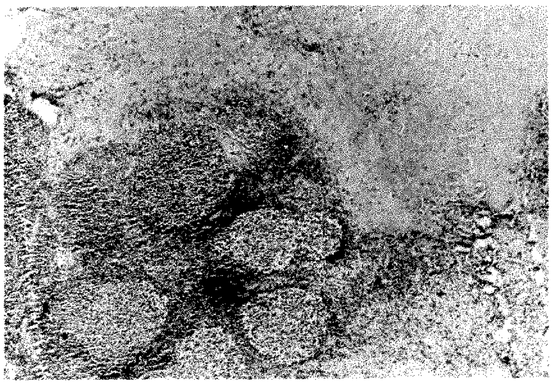

Fig. 5. Photomicrograph of irradiated lymph node containing cancer prior to irradiation. This area is now replaced by fibrous tissue but the remainder of the involved lymph node shows prominent germinal centers. (V. A. Neg. 3100A and 3100H.)

tients) in the group treated by low-dose preoperative irradiation.

When there was persistent carcinoma in both the tonsil and the cervical lymph nodes, the prognosis was extremely poor, and only six patients out of 35 survived (four of these survivors had one or two positive neck lymph nodes).

An operation following definitive radiation therapy salvaged 30 percent of the irradiation failures when viable tumor was found in the specimen (three out of ten patients). However, none of the patients failing after preoperative irradiation and operation was salvaged by additional radiation therapy.

The number of neck lymph nodes containing viable carcinoma correlated well with prognosis (Table IV). Patients with no tumor in the specimen or only one positive lymph node had survival rates in the range of 60 percent. In a group of 36 patients with two or three positive lymph nodes, the survival rate was approximately 25 percent. Patients with four or more positive lymph nodes had an extremely poor prognosis, less than ten percent surviving. These results are comparable for the patients treated by preoperative irradiation and surgery or irradiation alone, suggesting a lack of dose effect.

Analysis of Recurrences After Therapy: About 80 percent of the recurrences or distant metastases developed within 24 months from the initial treatment (Fig. 9). Patients with larger lesions developed recurrent tumor earlier than those with small tumors, and although not statistically significant, those treated by preoperative irradiation failed at a faster rate than those receiving irradiation alone.

Table V summarizes the percentage of failures at different sites, grouped by the stage of the patients treated by preoperative irradiation. Failure rates in the range of 25 percent to 30 percent were noted in the patients with T_1 and T_1, $N_{0,1,2}$ lesions. The marginal failure rate was about 15 percent–20 percent. Patients with $T_{1,2,3}$ and $N_{0,1,2,3}$ tumors had a higher failure rate (47 percent to 66 percent), and the number of recurrences at marginal sites was higher

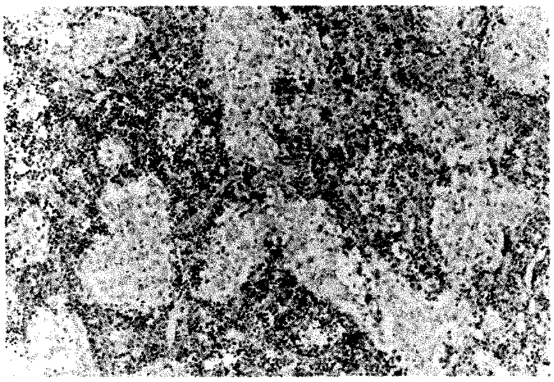

Fig. 6. Profound histiocytic reaction in lymph node following radiation therapy. (V. A. Neg. 3100D.)

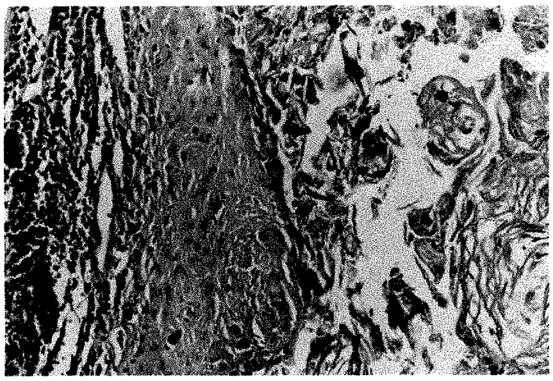

Fig. 7. Lymph node after 3,000 rads, showing only masses of keratin. (V. A. Neg. 3100I.)

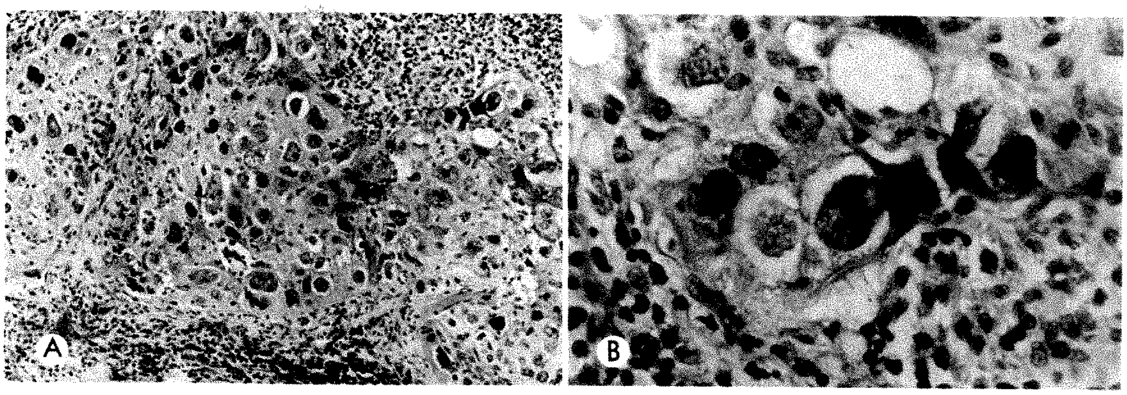

FIG. 8. (*A*) Persistent squamous cell cancer with keratinization after inadequate irradiation. This tumor was fairly deep in the tissue ("L") and also was growing in the salivary gland duct ("O"). (V. A. Neg. 3100L and 3100O.) (*B*) Persistent irradiated carcinoma in a lymph node. Individual tumor cells show profound nuclear aberrations which is better shown in "M." (V. A. Neg. 3100K and 3100M.)

(approximately 30 percent). Seven out of the eight patients with Stage IV lesions failed, six of them in the tonsil and marginal areas.

Table VI shows the recurrence rate for the patients treated by irradiation alone. This is not statistically different from those treated by preoperative irradiation. An unusually high failure rate was noted in the $T_{1,2}$–$N_{1,2}$ tumors, but this is probably related to the small number of patients (nine) and the development of distant metastases in two of them. The local failure rate was approximately 25 percent. In the patients with $T_{1,2,3}$ and $N_{0,1,2,3}$, the failure rate was 40 percent to 50 percent, and the local recurrence rate ranged between 23 percent and 31 percent. Twenty-one out of 27 patients with T_4 lesions (77 percent) failed after treatment, 70 percent of them developing local or marginal recurrences.

Distant metastases were relatively uncommon. Ten patients in the preoperative irradiation and surgery group were known to develop distant metastases, usually combined with other sites. As a reflection of the more advanced lesions treated by irradiation alone, 13 out of 97 patients developed metastatic disease, about half of them combined with other sites.

The extent of the primary tumor and marginal extensions was reflected in the recurrence rate (Table VII). Patients with lesions in the tonsil only had a failure rate of 20 percent in the preoperative group (three out of 15), and eleven percent in the

TABLE I

CARCINOMA OF THE TONSIL: ABSOLUTE THREE YEAR SURVIVAL, NED

	Preoperative Treatment*	Dead ICD	Irradiation Alone†	Dead ICD
$T_{1,2}$—N_0	11/17 (64.7 percent)	1	16/21 (76 percent)	2
$T_{1,2}$—$N_{1,2}$	11/22 (50 percent)	4	4/9 (44.4 percent)	—
T_3—$N_{0,1,2}$	18/42 (42.8 percent)	3	10/22 (45.4 percent)	2
$T_{1,2,3}$—N_3	3/9 (33 percent)	1	4/16 (25 percent)	2
T_4—Any N	0/8 (—)	—	3/27 (11 percent)	3

* 2 Patients refused surgery, treated by irradiation alone; 3 patients died before operation; 3 patients were inoperable after preoperative treatment.

† 3 Patients died during treatment, tabulated as failures.

NED = no evidence of disease.

ICD = intercurrent disease, no clinical evidence of tumor.

TABLE II

CARCINOMA OF THE TONSIL: HISTOLOGICAL CLASSIFICATION: THREE YEAR SURVIVAL, NED

Epidermoid Carcinoma	Preoperative Treatment				Irradiation Alone			
	T_1, T_2 $N_{0,1,2}$	T_3 $N_{0,1,2}$	$T_{1,2,3}$ N_3	T_4	T_1, T_2 $N_{0,1,2}$	T_3 $N_{0,1,2}$	$T_{1,2,3}$ N_3	T_4
A. Keratinizing								
Heavily Keratinized	1/2	1/2	—	—	0/1	1/1	—	—
Well Differentiated	2/2	2/5	0/1	—	3/4	—	—	0/1
Intermediate	7/14	8/18	1/1	0/3	7/10	2/5	1/3	0/5
Poorly Differentiated	2/5	1/2	—	0/3	2/3	3/7	0/2	1/6
B. Non-Keratinizing								
Well Differentiated	—	—	—	—	—	—	—	—
Intermediate	7/10	3/5	2/4	0/1	1/2	1/3	—	0/2
Poorly Differentiated	1/1	2/6	0/2	—	1/2	1/1	2/5	1/5
C. Unspecified	1/4	1/4	0/1	0/1	4/6	2/4	1/6	0/6
Lymphoepithelioma	1/1	—	—	—	2/2	—	—	—
Undifferentiated Carcinoma	—	—	—	—	—	0/1	—	1/2

irradiation alone group (two out of 17). Patients with extension into either the palate, the base of the tongue, or in the pharyngeal wall, had a recurrence rate of approximately 30 percent. However, those with larger lesions extending into the soft palate and the base of the tongue, or in the latter location combined with the lateral pharyngeal wall, developed recurrences in about 50 percent of the cases. There was

TABLE III

CARCINOMA OF THE TONSIL: STATUS OF PATHOLOGICAL SPECIMEN AND SURVIVAL

	Preoperative Treatment				Irradiation Alone*			
	3 Years				3 Years			
	$T_{1,2}$ $N_{0,1,2}$	T_3 $N_{0,1,2}$	$T_{1,2,3}$ N_3	T_4	$T_{1,2}$ N_0	T_3 $N_{0,1,2}$	T_3–N_3	T_4
Neg. primary Neg. neck lymph nodes	16/19	10/11	2/2	0/1	3/3	2/2	—	—
Neg. primary Pos. neck lymph nodes	2/3†	0/2	—	0/1	1/2	1/2	1/2	0/1
Pos. primary Neg. neck lymph nodes	2/4	3/7	0/1	0/2	0/3	—	—	—
Pos. primary Pos. neck lymph nodes	2/11†	4‡/17	0/4	0/3	0/1	0/1	—	—
Operation not done	0/1	1/4	1/2	0/1	15/21	7/17	2/14	2/26
Information not available	0/1	0/1						

* Patients treated by irradiation, subsequent operation for suspected persistent or recurrent tumor.

† Two patients with only one positive neck lymph node, one with two neck lymph nodes.

‡ Only one or two positive neck lymph nodes.

Table IV

CARCINOMA OF THE TONSIL: NUMBER OF POSITIVE LYMPH NODES IN INITIAL PATHOLOGIC SPECIMEN AND ABSOLUTE SURVIVAL, NED

No. of Positive Nodes	Preoperative Treatment		Irradiation Alone	
	3 Years	5 Years	3 Years	5 Years
0	31/45 (68.8 percent)	24/36 (66.6 percent)	5/8	5/7
1	6/10 (60 percent)	3/6 (50 percent)	2/3	2/3
2–3	4/15 (26.6 percent)	3/13 (23 percent)	1/4	1/4
4 or More	1/17 (5.8 percent)	1/14 (7 percent)	1/2	0/1

no significant difference in the percent of patients showing recurrent tumor in the various locations, whether they were treated by preoperative irradiation and surgery or irradiation alone.

Table VIII summarizes the incidence of lymph node recurrences depending on the initial clinical stage of the lymph nodes. The failure rate is similar for the patients treated by preoperative irradiation or irradiation alone. Either modality yielded a recurrence rate of ten percent to 20 percent in patients with N_0 or N_1 lymph nodes, and 25 percent to 30 percent in patients with N_2 or N_3 lymph nodes. Ten percent of the patients treated by preoperative irradiation and surgery developed contralateral lymph node metastases, whereas only one patient in the irradiation alone group failed in the opposite neck (one percent).

Complications and Causes of Death: Table IX shows the causes of death in the two groups of patients, regardless of the time this occurred during or after treatment. Tumor recurrence and related effects were the major cause of death in 47 patients in each of the two groups. A significantly greater number of fatal complications was noted in the preoperative group (six) as opposed to the irradiation alone group (two—one of them a patient operated upon for suspected persistent tumor). Seven patients in each of the two groups developed a fatal second primary tumor, most of them located in the lung or esophagus. Fourteen of the patients in the preoperative group and 16 in the irradiation alone group died of intercurrent disease, without clinical evidence of tumor.

Table X shows the complications in the patients treated by preoperative irradiation. Three developed a carotid rupture following surgery, one a postoperative pneumonia, and one died of a cerebrovascular accident. One patient died during the postoperative period, but the exact cause of death could not be determined. Significant non-fatal complications were recorded in 18 patients. In seven instances, a pharyngocutaneous fistula occurred, which usually improved with conservative management. In two patients, surgical correction with a pedicle skin graft was required. Osteomyelitis of the mandible was noted in four patients. In general, preoperative irradiation produced slightly longer healing periods than those observed in non-

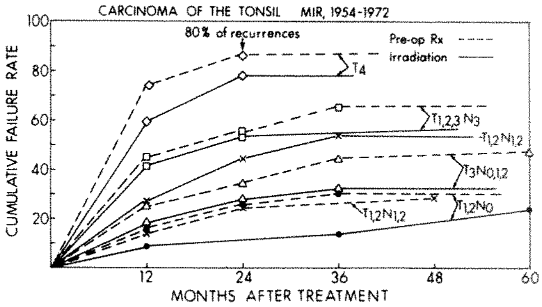

Fig. 9. Cumulative failure rate according to anatomical stage on patients treated by either preoperative irradiation and surgery or irradiation alone. Failures appeared more rapidly in patients receiving the combined treatment, although differences are not statistically significant. (W. U. Neg. 75-4347.)

TABLE V

CARCINOMA OF THE TONSIL: SITES OF KNOWN TUMOR RECURRENCE: PREOPERATIVE IRRADIATION

	$T_{1,2},N_0$	$T_{1,2},N_{1,2}$	$T_3,N_{0,1,2}$	$T_{1,2,3},N_3$	T_4
Total no. of patients	17	22	42	9	8
Number patients failing	5	8	20	6	7
Percent patients failing	29	36	47	66	87
Local	1*	1*	2§		
Local, marginal, or both	2 }23 percent	3 }14 percent	4‖		2‡ }75 percent
Marginal and ipsilateral neck lymph nodes	1†	1	4 }28 percent	1 }33 percent	4
Marginal and distant metastases			4	2	
Ipsilateral neck lymph nodes	1	1		2	
Contralateral neck lymph nodes	2†	1	4¶		1‡
Distant metastasis	—	1	1	1	1
Opposite tonsil	1		1¶		

* Patients refused surgery.
† 1 Patient, recurrence in base of tongue and both necks.
‡ 1 Patient, marginal recurrence and contralateral neck.
§ 2 Patients died before operation.
‖ 1 Patient inoperable, treated by radiation therapy alone.
¶ 1 Patient, cancer opposite tonsil and neck 4 years after treatment.

irradiated patients, but this has not been a significant problem with preoperative doses of 3,000 rads. Substantial delayed wound healing, probably secondary to irradiation, was noted in three patients. Xerostomia, bothersome to the patients, was reported in three instances and two patients complained of significant difficulty swallowing for a long time after their surgery.

Table XI details the complications in the patients treated by irradiation alone. One patient developed a massive recurrence and carotid rupture following therapy. One patient died of a cerebrovascular accident following surgery for suspected persistent tumor several months after irradiation. Severe non-fatal complications were recorded in 23 patients. Three instances of osteonecrosis of the mandible were noted. Three patients developed pharyngocutaneous fistula following operations for suspected persistent tumor. Severe dental

TABLE VI

CARCINOMA OF THE TONSIL: SITES OF KNOWN TUMOR RECURRENCE: IRRADIATION ALONE

	$T_{1,2},N_0$	$T_{1,2}, N_{1,2}$	$T_3,N_{0,1,2}$	$T_{1,2,3}, N_3$	T_4
Total no. of patients	21	9	22	16	27
Number patients failing	5	6	9	8	21
Percent patients failing	24	66	41	50	77
Local	2	1			5
Local and marginal	1 }19 percent		1		2
Local and ipsilateral neck lymph nodes	1	}27 percent	1	3	5 }70 percent
Local and contralateral neck lymph nodes			}22.7 percent	1 }31 percent	
Local and distant metastases		2	1		3
Marginal			2	1	2
Ipsilateral neck lymph nodes	1	1	2	2	2
Distant metastasis		2	2	1	2

Table VII

CARCINOMA OF THE TONSIL: EXTENT OF PRIMARY TUMOR AND INCIDENCE OF LOCAL RECURRENCE

	Preoperative Treatment	Irradiation Alone
Tonsil (including pillars)	3/15 (20 percent)	2/17 (11 percent)
Tonsil and soft palate	8/30 (26 percent)	7/21 (33 percent)
Tonsil and base of tongue	5/18 (27 percent)	3/9 (30 percent)
Pharyngeal wall	3/9 (30 percent)	3/9 (30 percent)
Tonsil, soft palate and base of tongue	10/22 (45 percent)	13/27 (48 percent)
Base of tongue and lateral pharyngeal wall	2/3 (67 percent)	3/6 (50 percent)
Nasopharynx	1/1 —	4/8 (50 percent)

decay was noted in four patients and long standing severe xerostomia in seven patients. Three patients complained of appreciable difficulty swallowing, and edema of the larynx with some hoarseness was noted in two patients. One patient developed pneumonia during radiation therapy.

DISCUSSION

The treatment of carcinoma of the tonsil has been primarily by radiation therapy and with combinations of megavoltage beams, improved survival rates have been reported.[1,8,13,15,17,21] A few authors have advocated a surgical procedure, alone or combined with irradiation, as the primary treatment.[2,4,5,12,22] The incidence of failure at the primary site and neck has been reported to be as low as 20 percent by Whicker *et al.*[22] but local failure rates as high as 41 percent have been described.[20]

Several reports have indicated that irradiation alone is very effective in sterilizing small tumors (T_1, and to a lesser extent, T_2), but recurrence rates in the range of 30 percent to 50 percent have been noted in patients with T_3 and T_4 tumors, usually with doses in the range of 6,000–6,500 rads in six to six and one-half weeks.[8,21] Shukovsky and Fletcher[17] showed a consistent dose-response in patients with carcinoma of the tonsillar fossa, depending on the stage of the tumor, and they pointed out

Table VIII

CARCINOMA OF THE TONSIL: CLINICAL LYMPH NODE STAGING AND PERCENTAGE OF NODAL RECURRENCE

	Preoperative Treatment			Irradiation Alone		
	No. of Patients	Recurrences		No. of Patients	Recurrences	
		Ipsilateral	Contralateral		Ipsilateral	Contralateral
N_0, T_1, T_2	17	2 (11 percent)	1 (8 percent)	21	— —	—
T_3, T_4	18	2	2	12	2 (6 percent)	—
N_1, T_1, T_2	16	1 (14 percent)	— —	5	1 (23 percent)	—
T_3, T_4	20	4	3 (8 percent)	16	4	—
N_2, T_1, T_2	5	1 (25 percent)	— —	4	1 (30 percent)	—
T_3, T_4	11	3	1 (9 percent)	6	2	—
N_3, T_1, T_2	9	2 (27 percent)	1 (11 percent)	1	— —	—
T_3, T_4	2	1	— —	32	10 (30 percent)	1

TABLE IX

CARCINOMA OF THE TONSIL: CAUSES OF DEATH (UNLIMITED TIME)

	Pre-operative Treatment	Irradiation Alone
Total no. of patients	98	97
Tumor recurrence	47	47
Complications	6	2*
Second primary tumors		
Nasopharynx		1
Lung	3	3
Esophagus	3	3
Breast	1	
Intercurrent disease	14	16

* One patient, massive tumor in tonsil and carotid rupture.

One patient operated on for suspected persistent tumor developed a postoperative cerebrovascular accident.

One additional patient in preoperative treatment group developed a second primary in the epiglottis, surviving NED 3 years after treatment.

that although doses of irradiation in the range of 6,000–6,500 rads may be adequate to control the tumor in T_1–T_2 lesions, they are not effective in sterilizing larger tumors, and higher doses in the range of 7,000–7,500 rads in seven to eight weeks are necessary for T_3 and T_4 lesions. In their series, the local recurrence rate in T_1 lesions was none, in T_2, 14 percent, T_3, 21 percent and T_4, 38 percent. The patients with T_3 or T_4 lesions receiving 6,000–6,500 rads showed a recurrence rate of 50 percent, whereas the figure decreased to only 19 percent when more than 6,500 rads were given. It is evident that since in our material a significant proportion of the patients were treated over a long period of time with doses as low as 5,500 rads prior to 1968, a larger percent of failures would be observed.

A report by Maltz *et al.*,[12] in a group of 36 patients with carcinoma of the tonsil treated by preoperative irradiation (4,000–4,500 rads) and *en bloc* dissection of the primary tumor and neck, showed an absolute survival of 56 percent and a determinate survival of 67 percent. The survival rate for T_1 lesions was 80 percent, for T_2 69 percent and for T_3, 33 percent. These results are not statistically different from those reported in this paper with preoperative irradiation or irradiation alone.

The analysis of data available, including that reported herein, fails to show any significant improvement in cure rates or tumor control in carcinoma of the tonsil with a combined approach. It must be emphasized that a judiciously indicated surgical resection following definitive radiation therapy, when there is persistent or recurrent tumor at the primary site or the neck, will salvage about 30 percent of the irradiation failures. It is obvious that radiation therapy alone has not been greatly successful in controlling carcinoma of the tonsil in more advanced stages. In our experience, marginal failures after definitive irradiation were noted in ten patients, most of them with advanced lesions (T_3–T_4), which may be a reflection of a geographical miss or inhomogeneities of the dose distribution. In the larger lesions, the lower doses used in earlier years very likely are responsible for these failures. As indicated by Gelinas and Fletcher,[10] in 125 patients with tonsillar carcinoma, the failure to control the tumor was due to a geographical miss in five patients, underdose in seven patients, but in eleven, they found no obvious reason.

In the preoperative group reported here-

TABLE X

CARCINOMA OF THE TONSIL: PREOPERATIVE IRRADIATION COMPLICATIONS (UNLIMITED TIME)

Fatal	
Carotid rupture	3
Postoperative pneumonia	1
Postoperative cerebrovascular accident	1
Postoperative death, undetermined cause	1
Non-Fatal	
Transient fistula	7
Osteomyelitis of mandible	4
Delayed wound healing	3
Xerostomia	3
Significant swallowing difficulty	2

in, marginal failures were identified in 26 patients, 18 of them with T_3 or T_4 lesions. This is probably due to a limitation in the amount of tissue that can be removed by the surgical procedure. Also, since these lesions show appreciable regression following preoperative irradiation, there may be an inclination on the part of the surgeon to decrease the magnitude of the resection necessary to remove all micro-extensions of the tumor. In order to avoid this, it is recommended that prior to the initiation of radiation therapy, a tatooing with Indian ink be performed indicating the volume that would be removed if the operation was to be performed at that time and that no reduction be made following the partial regression of the tumor induced by the irradiation. Equally helpful are meticulously drawn diagrams showing the tumor extent at the initial evaluation.

Either preoperative irradiation and a neck dissection or radiation therapy alone to doses in the range of 6,000–6,500 rads were equally effective in achieving the same tumor control in the necks. The ten percent failure rate noted in the opposite neck non-irradiated in the patients treated by preoperative irradiation and surgery is consistent with data reported previously.[3] The absence of contralateral neck failures in the patients treated by irradiation alone to doses in the range of 5,000–6,000 rads confirms the effectiveness of these doses of irradiation in controlling subclinical disease.[9]

A greater number of fatal complications was noted in the group treated by preoperative irradiation than in those treated by irradiation alone. However, the incidence of preoperative fistula or interference with wound healing has not been greater than that reported in patients treated by a surgical procedure alone for tumors of the head and neck.[4] The incidence of osteonecrosis of the mandible was approximately the same in both groups (three to four percent). This is considerably less than has been reported by others,[6,11] but this is probably due to the somewhat lesser doses of irradiation administered for several years and the consistent use of 22 MeV photons to deliver 50 percent of the dose to the upper portals which included the primary tumor and the upper neck. The majority of the patients reported by Grant and Fletcher[11] and Cheng and Wang[6] received doses to the mandible of more than 6,500 rads in 30 fractions/6–7 weeks and were treated with single portals or unequal loading on Co^{60} teletherapy units.

Xerostomia and changes in the saliva causing severe dental decay are more frequent in the patients treated by irradiation alone. Although the dryness of the mouth may persist for prolonged periods of time, the dental decay can be prevented or significantly diminished by prophylactic fluoridation repeated periodically and by appropriate dental care, particularly when extractions or operative procedures are necessary following irradiation.[7] Also, the removal of any severely diseased teeth and treatment of periodontal disease prior to the initiation of radiation therapy will significantly decrease these complications, including the osteomyelitis of the mandible, which in two of the patients in this series,

TABLE XI

CARCINOMA OF THE TONSIL: RADIATION THERAPY ALONE: COMPLICATIONS (UNLIMITED TIME)

Fatal	
Died during treatment, undetermined cause	2
Carotid rupture*	1
Postoperative cerebrovascular accident†	1
Non-Fatal	
Severe xerostomia	7
Severe dental decay	4
Osteonecrosis of mandible	3
Fistula†	3
Difficulty swallowing	3
Edema of larynx	2
Pneumonia	1

* Massive tumor.

† Operation for suspected persistent tumor.

followed dental extractions after irradiation.

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INITIAL COMPARATIVE RESPONSE TO PEAK PIONS AND X-RAYS OF NORMAL SKIN AND UNDERLYING TISSUE SURROUNDING SUPERFICIAL METASTATIC NODULES*

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ABSTRACT:

Given the limitations of available material and methods for measuring skin response, the relative biological effectiveness (RBE) for the development and healing of skin reaction to pions in this experiment is 1.43. This is based on data obtained from a patient with malignant melanoma, in whom multiple skin nodules and the surrounding normal skin were randomized into three dose levels for pions and x-rays. The RBE for skin reaction was obtained while the skin tumor nodules appeared to regress at least as rapidly with pion therapy as with x-rays. Without benefit of adequate observation of time required for nodule regrowth, any estimate of tumor RBE is speculative.

HUMAN radiobiological experiments using metastatic tumor nodules in the skin and the surrounding normal skin were begun at the Clinton P. Anderson Meson Physics Facility in Los Alamos on October 21, 1974. The objective of these experiments was to observe and compare the responses of the epithelium and the subcutaneous tissues in the high linear energy transfer (LET) portion of the pion stopping region with responses of those tissues to x-radiation. Another objective was to obtain information on the relative response of human tumors to peak pions as compared with x-rays. A preliminary estimate of the high-LET portion of the pion peak had been previously determined from physical measurements.[1,8] A depth-dose biological response curve had been established with a cell system, and the response of an experimental mammary adenocarcinoma had been investigated.[6,9] Although all these data require refinement, sufficient information was believed to exist for cautious exploration of human tissues and tumors.

Since safety was the principal restriction in planning these first human experiments, the tolerance of the normal tissues to superficial x-rays was used as a guide to dose levels. First, modest doses (60 percent of skin tolerance for superficial x-rays) were fractionated over an eight day period. When no untoward acute effects were seen in the normal tissues, a second series of tests was conducted using doses at 75 percent of skin tolerance. In each instance, peak pion doses were given at one-half the daily rate and total dosage. Since the individual doses given in eight days appeared to be tolerated over the acute observation period, the experiment reported here was performed. This test was designed to establish a dose-response curve for peak pions in the high-LET region as compared with

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140 kVp x-rays. The selected fractionation schedule matched a curative clinical schedule. Although this represents a preliminary report, the data appear to be of sufficient interest for presentation at this time.

MATERIAL AND METHOD

Patient eligibility for this program required the presence in the skin of two or more metastatic tumor nodules not exceeding 3 cm in diameter. In this experiment, a single patient with malignant melanoma was the subject. Resulting dose response curves were based on 13 weeks of observation. Twenty-seven skin nodules were assigned serial numbers. Eighteen of these nodules between 5 and 16 mm in diameter were randomly assigned to six groups of three nodules each. The dose levels were not intended to exceed skin tolerance. Three groups of nodules were given total surface x-ray doses corresponding to 55, 66, and 75 percent of 5,200 rads, 15 fractions in 19 days. The other three groups were treated with peak pions. Total pion doses were 50 percent of the x-ray doses at the three levels. Most of our data indicated that the maximum biological effect occurred slightly downstream from the true physical peak.[9] This finding was in reasonable agreement with measurements of beam quality with and without collimators by Richman[8] and by Amols and Dicello.[2] Therefore, the skin surface was placed at the physical peak, with the center of the tumor nodule downstream from the physical peak. A 3 cm diameter collimator was used for all pion-treated skin nodules. The x-ray collimator was 3 cm in diameter for all nodules so treated, except for one 5 cm collimator in the 55 percent group.

The x-ray machine was operated at 140 kVp with a half value layer of 2.6 mm aluminum. The dose rate was 500 rads per minute. The peak pion dose rate varied from five to seven rads per minute. Dosimetry for pions[5] was performed with 0.1, 0.5, and 1.0 cc thimble-type ionization chambers and with small parallel plate chambers constructed from Shonka-150 plastic. Because of the size of the stopping region, most of the information was obtained from 0.1 cc chambers to minimize the perturbation of the radiation field during measurements. Data from the larger chambers were used to determine the error introduced by the chamber volume. Measurements were taken of absorbed dose as a function of depth below each collimator, and beam profiles in the plane perpendicular to the beam axis were measured in a water phantom. A three-dimensional, remotely controlled scanner, accurate to 0.01 cm, was used to position the chamber during measurements. The data obtained by these physical measurements were sufficiently accurate to allow placement of the beam, with respect to the surface of each collimator, within a fraction of a millimeter. The change in dose as a function of depth below the collimator was similar for x-rays and pions to depths of at least 0.5 cm. The beam profile across the 3 cm collimator was essentially flat for x-rays over a central diameter of 2.3 cm. The profile for pions was approximately Gaussian, with a full width at half maximum of about 3 cm. A dosimetric check was made before and after treatment each day and whenever there was an interruption in accelerator operation necessitating replacement of parts.

To estimate the whole body dose, we measured the absorbed dose and radiation quality with 2.5 cm spherical proportional counters[3] outside the stopping region at several positions. The absorbed dose resulting from neutrons was typically about 0.02 percent of the peak dose. The absorbed dose for low-LET radiation, primarily muons or electrons, or both, from the primary beam, was between 0.01 and 0.1 percent of the peak dose.

A decision was made that, should the biomedical channel not be operative on a particular scheduled treatment fraction day, the nodules to be treated with pions would be treated with a dose of x-rays corresponding to the appropriate percentage of curative dose level for the particular nodule. On day 12, the day for delivery of the tenth fraction, the channel failed for six of the pion nodules, two at each of the three dose levels. Accordingly, those nodules were given the dose of x-rays which they would have received had they been in a corresponding x-ray group. The total doses of x-rays and pions delivered over the 19 day period in 15 equal fractions are shown in Table I.

Skin response was monitored three ways: (1) eight female artists and art teachers periodically estimated the skin color changes and reactions on a scale of one to seven; (2) color photographs were made at least twice a week of each of the 18 areas using constant lighting and exposure factors; and (3) clinical notations were made by the radiation therapists. The artists and art teachers were instructed in scoring the skin reactions in each of the treated areas according to a pre-determined color scale. Once instructed, they were not allowed to discuss their observations with the physicians, nursing staff, or themselves. Individually, they viewed the nodules, marked their score sheets, and sent each sheet directly to the project statistician. The nodules were marked in such a way that the observers would not be able to distinguish pion-irradiated nodules from x-irradiated nodules.

In the second observation method, photographs were taken using high-speed Ektachrome tungsten film with 85B filter and bounce electronic flash supplementing a mixture of warm and cold fluorescent overhead lighting. The magenta and yellow-forming layers of this film are sensitive in the range of 400 to 580 nanometers. This is adequate for the absorption bands of hemoglobin, which range from 415 to 575 nanometers.[4] Optical density was measured from the photographs, using a McBeth densitometer, Model 504, with Kodak Filter 58 (green). This filter is most sensitive for wavelengths in the absorption band range of hemoglobin. Thus, this combination of film and filter provided optical density measurements which increased with the degree of erythematous skin reaction. The skin adjacent to each treatment area was adjusted to zero on the densitometer, and the optical density of the treated area was measured. The raw data (Table II) were averaged and plotted for each of the 13 weeks of observation, giving three curves each for x-ray and pion radiation (Fig. 1). The two 75 percent curves were then plotted on a separate graph (Fig. 2). In each case, the dose specified is the peak dose under the collimator. Dose response curves were obtained by plotting average values for the maximum skin effect and calculating a least squares fit (Fig. 3). These curves were linearly interpolated to determine the pion and x-ray doses that would produce an optical density of 0.23, and the ratio of these doses was used to calculate skin relative biological effectiveness (RBE). (The x-ray curve had to be extended only 77 rads, or 7.4 percent of the x-ray dose range, to intercept this optical density.)

The radiation therapists were unable to measure the tumor nodules consistently by the use of calipers. Therefore, their clinical impressions were used, which were consistent among the three parties.

Table I*

Level (percent)	X-Ray Rads		Peak Pion Rads	
	Daily	Total	Daily	Total
55	191	2,860	95	1,430
66	229	3,432	114	1,716
75	260	3,900	130	1,950

* Total doses of x-rays and pions delivered over a 19 day period in 15 fractions to 18 tumor nodules, randomly assigned to one of three dose levels. The pion doses were 50 percent of 55, 66, and 75 percent of 5,200 rads in 19 days, 15 fractions.

RESULTS

The clinical observations of the artists and art teachers were so inconsistent as to preclude analysis. However, the clinical observations of the radiation therapists and the optical density measurements indicated that maximum erythema occurred during the fifth, sixth, or seventh week for

Table II*

Weeks	0	1	2	3	4	5	6	7	8	9	10	11	13
1	.00	.05	.14	.16	.20	.35	.47	.35	.16	.20	.19	.22	.18
2	.00	.01	.07	.10	.12	.23	.27	.26	.17	.13	.13	.19	.16
3	.00	.10	.05	.17	.10	.19	.10	.18	.10	.15	.12	.16	.05
4	.00	.08	.01	.07	.10	.22	.24	.25	.20	.19	.10	.06	.08
Nodule 5	.00	.04	.10	.10	.12	.14	.15	.17	.10	.12	.11	.05	.06
6	.00	.02	.08	.09	.16	.21	.22	.19	.20	.23	.10	.20	.08
7	.00	.00	.16	.10	.16	.17	.25	.29	.23	.17	.15	.17	.15
8	.00	.00	.02	.07	.13	.13	.10	.15	.14	.10	.08	.06	.03
9	.00	.05	.00	.09	.10	.20	.21	.21	.21	.15	.07	.07	.09
10	.00	.02	.16	.22	.35	.48	.44	.22	.23	.17	.19	.23	.24
11	.00	.02	.08	.11	.17	.28	.27	.26	.11	.15	.12	.16	.11
15†	.00	.11	.07	.17	.39	.42	.55	.31	.26	.34	.39	.17	.22
16	.00	.04	.05	.06	.10	.21	.20	.25	.20	.10	.10	.19	.10
17	.00	.11	.12	.15	.19	.41	.31	.34	.31	.30	.36	.17	.20
18	.00	.04	.07	.14	.12	.12	.15	.19	.11	.13	.11	.10	.12

* Raw data obtained by measuring optical density of photographs of skin nodules treated with x-rays or pions over a 13 week observation period. A McBeth densitometer, Model 504, with Kodak Filter 58 (green), was used to obtain the data. The densitometer was adjusted to zero on the skin adjacent to each treatment area, and the optical density of the treated area measured.

† Accurate optical density measurements of Nodule 12 (66 percent pion), Nodule 13 (55 percent pion), and Nodule 14 (55 percent x-ray) could not be obtained due to excessive hair.

pion and x-radiation. The ratio of doses obtained by averaging the optical densities resulted in a relative biological effectiveness (RBE) for skin erythema of 1.43 at the optical density of 0.23.

The radiation therapists all felt that the tumors treated with pion radiation regressed at least at the same rate as those irradiated with x-rays and that the nodules became softer somewhat more quickly, and this is in agreement with the observations made on the earlier mammalian adenocarcinoma tests.[6]

Approximately 15 weeks after the start of treatment, one of the nodules appeared to have started regrowth. This nodule had been treated with pions at the 55 percent dose level. However, during treatment and the subsequent observation period, it had remained palpable. Approximately 17 weeks after the start of treatment, a nodule treated with pions at the 66 percent dose level appeared to have started regrowth. At this writing, no regrowth has been observed in any other nodules. With such limited data regarding regrowth, information regarding comparative tumor effects must be limited.

At this intermediate period of observation, six months after the first patient was treated, and four and one-half months since the last treatments, no evidence of any unusual untoward effects in the epidermis or subcutaneous tissues has been observed in any of the patients treated in this series of tests.

DISCUSSION

The primary purpose of this series of human radiobiological experiments was to check the response of skin and subcutaneous tissues to pion radiation in comparison with x-radiation. The optical density measurements corresponded with our clinical observations. Consultation with the Eastman Kodak Corporation Research Laboratory[7] indicated that the optical density technique used for this experiment was most reliable during the increase in the acute erythematous reaction, from which dose response curves were derived (Fig. 3). Although the erythematous reaction varied dose for dose in different skin areas, the relative difference between normal skin and irradiated skin could be adequately quantified by setting the densitometer to zero for the normal skin adjacent to the treated

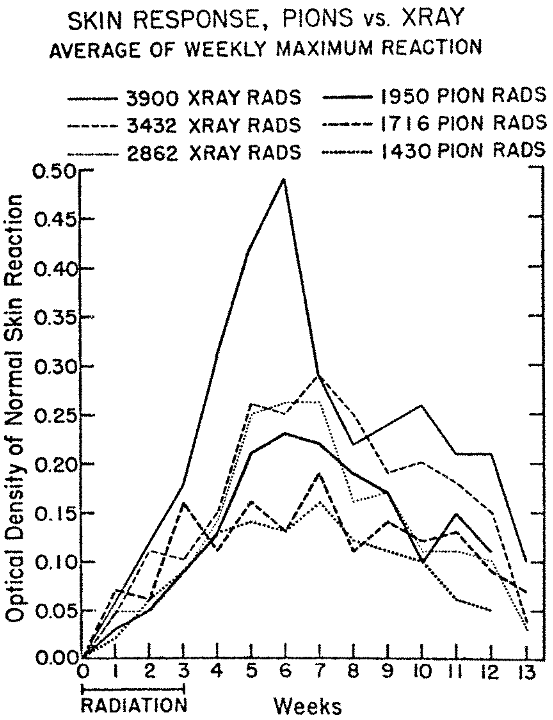

Fig. 1. Average values for pions and x-rays at each of three dose levels, plotted for each of 13 weeks of observation. Data were derived from Table II. X-ray doses were based on 55, 66, and 75 percent of a skin tolerance dose of 5,200 rads in 19 days, 15 fractions. Pions were given at 50 percent of the x-ray dose.

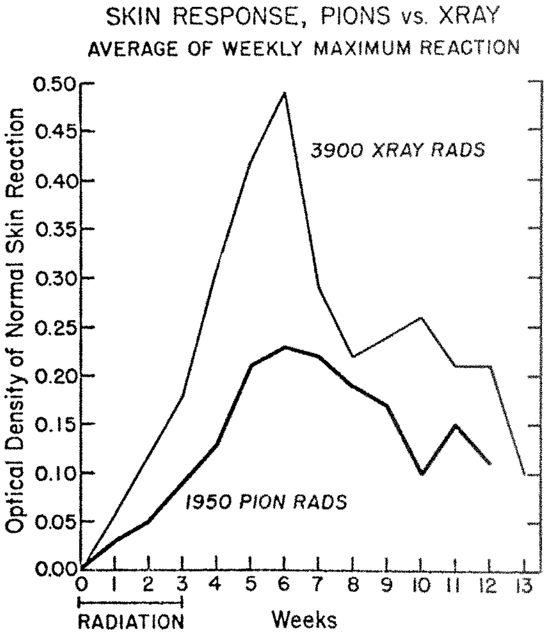

Fig. 2. Average optical density values for pions and x-rays at the 75 percent level only. This was the maximum given in this test series.

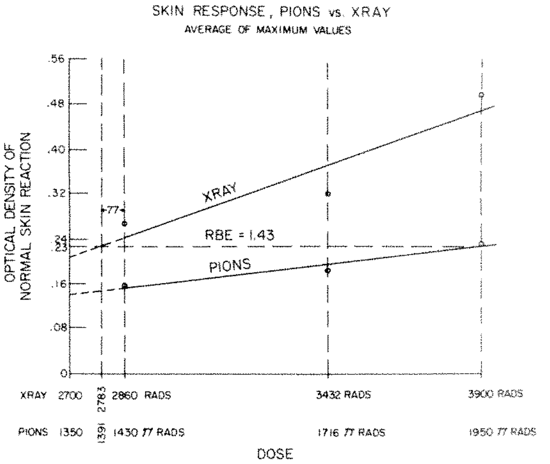

Fig. 3. A graph of the least squares fit for both the pion and x-ray points representing average values for the maximum skin effect at each dose level. By linearly interpolating those curves, the RBE for acute skin reaction is 1.43.

areas.[7] Some bias may well be likely, however, due to the subjective selection of the points on the untreated skin at which the densitometer was set to zero. The Kodak Laboratory staff indicated, however, that different filters and film would provide more accurate measurements once secondary changes in skin (such as excessive tanning or dry desquamation) take place.

The clinical observations of the radiation therapists supported the optical method as an objective measure, in that the radiotherapists had no difficulty in observing the differences in the intensity of the skin reactions in each treatment area. There was little difficulty in detecting changes throughout the course of treatment and the ensuing observation period. At all dose levels, skin reactions to x-rays were observed as more intense than those produced by pions, although it is possible that this is due to differences in uniformity of dose in the treatment field. It is most probable that any uncertainty of the test results is associated with the size of the areas where maximum skin reaction occurred, rather than with the validity of the densitometric measurements or clinical observations. The surface dose distribution across the 3 cm x-ray field was greater than 90 percent in the central area of 4.15 cm^2. However, the central high dose area of the pion beam was only 1.63 cm^2. This decreased area of high dose for pions as compared to x-rays may have contributed to a decrease in maximum reaction in the pion fields. In our next series, a compensating filter will be built for the 140 kV x-ray unit to duplicate the pion surface dose so that the importance of this difference in surface dose can be evaluated.

It is of interest that our attempt to use untrained observers with good color sensing ability to implement the Bewley clinical observation technique ended in failure. To protect the color observers from possible bias on the part of physicians, the observers were not permitted to discuss their work once initial instructions as to coloration and other skin reactions were given. After the observation period ended, the statistician found he was unable to analyze the data provided by the observers because of inconsistencies. It is hoped, however, that a retraining session before the next skin nodule trials will turn this effort into a profitable venture.

The radiation therapists were disappointed by their inability to obtain consistent results from caliper measurements of the tumors. All of the tumors appeared to lose little in their diameter but decreased in height and became either flush with the skin or, occasionally, became slightly concave with respect to the skin surface at the time of their maximal regression. It should be noted that tumor nodule number nine differed somewhat from other nodules in that it was extremely hard. This nodule regressed a little more slowly, but continued to regress for a period of four weeks after the end of treatment and became flat like all others. It was quite clear that the regression of tumor was at least as marked with pion irradiation as with x-irradiation. However, an estimate of tumor RBE is hazardous without adequate regrowth information. Two of the pion-irradiated nodules have started regrowth as of this writing, but regrowth data are not adequate for statistical analysis.

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INITIAL EVALUATION OF REDUCED FRACTIONATION IN THE IRRADIATION OF MALIGNANT EPITHELIAL TUMORS*

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ABSTRACT:

From July, 1971, through June, 1974, 170 patients underwent radiation therapy with reduced fractionation at the Milwaukee County General Hospital and the Wood Veterans Administration Hospital. One or two fractions per week were delivered for five to seven weeks to a total dose based on the tolerance of normal tissues predicted by the nominal standard dose (NSD) hypothesis of Ellis. Three groups of patients were selected from this heterogeneous population for detailed analysis—carcinomas of the skin, breast, and lung. The 72 patients evaluated provide useful data in regard to acute and subacute reactions. Short term assessment of local tumor control in relation to surrounding normal tissue response is similar to that with conventional fractionation for each of these malignant epithelial tumors.

IN 1971, Dr. Frank Ellis joined The Medical College of Wisconsin as Director of Radiation Therapy, and fractionation patterns became more experimental in an attempt to test the nominal standard dose (NSD) hypothesis clinically and to learn whether or not it is indeed a guide to predicting short term and late morbidity as well as local tumor control. Obviously, there is much to be gained if the multiple variables of number of fractions, dose per fraction, interval between fractions, interruptions and gaps in therapy, dose rates, and integration of teletherapy and brachytherapy irradiation could be related to a single formula. The solution of every detail for a clinical course of irradiation is not to be expected from a single formula, but this could mark an advance from present fractionation patterns which are an empirically developed and poorly understood process often failing to provide answers to perplexing clinical problems. The question which must be asked of the hypothesis is whether or not it is a reasonable guide to the clinical treatment of cancer patients. This paper should be considered only as a preliminary retrospective review of patient material in an attempt to answer the above question and perhaps to stimulate others to formulate planned trials which may lead to more definite answers and ultimately a better understood approach to treatment.

MATERIAL AND METHOD

Approximately 600 patients have been treated with fewer than five fractions per week during the past four years. The patterns have generally fallen into three categories as seen in Table I. By far, the largest group treated is in the (A) category but since this seems reasonably close to existing patterns of 1,000 rads per week, this review chose to focus on the more radical departure from the conventional pattern, *i.e.*,

TABLE I

REDUCED FRACTIONATION PATTERNS
1971–1975

A—300 rads, 3x/wk., 18 fractions = 5,400 rads or 1,800 rets
B—405 rads, 2x/wk., 12 fractions = 4,860 rads or 1,800 rets
C—680 rads, 1x/wk., 6 fractions = 4,080 rads or 1,800 rets

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the (B) and (C) groups. The (A) group will be the subject of a separate communication.

In general, the doses expressed are minimal tumor doses, midplane doses, or doses at the point of intersection of the central axes. Complete dose distributions show less than ten percent variation from the expressed dose at other points in the target volume. The modalities utilized were 6 MeV and 25 MeV photons, electrons varying from 10 MeV–25 MeV, and conventional orthovoltage x-rays ranging from 120–280 kVp.

All NSD values were calculated using the Ellis formula.[2,3] The NSD value at Milwaukee County General Hospital during this period for megavoltage techniques was accepted as 1,800 rets. The NSD equation is defined as follows:

$TD = NSD \cdot N^{0.24} T^{0.11}$
$TD =$ Total dose in rads.
$d =$ Dose per fraction.
$N =$ Number of fractions required for the NSD.
$T =$ Elapsed time in days (day $1 = 0$) between first and last fraction.
$NSD =$ Estimated biological tolerance dose in rets for normal connective tissue.
$Ret =$ Rads equivalent therapy.

A. For example, to find the dose per fraction for treatment to be given twice weekly for six weeks, the following calculation was made:

$$\begin{aligned} TD &= NSD \cdot N^{.24} T^{0.11} \\ &= 1{,}800 \cdot 12^{0.24} \cdot 40^{.11} \\ &= 1{,}800 \cdot 1.81553 \cdot 1.50046 \\ &= 1{,}800 \cdot 2.724 \\ TD &= 4{,}903 \text{ rads} \end{aligned}$$

T—depends on day of week therapy is started.
Tues.—37 days
Thurs.—40 days
Since total dose (TD) = Number of fractions (N) × dose per fraction (d).

$$\begin{aligned} N \cdot d &= 4{,}903 \\ d &= \frac{4{,}903}{12} \\ &= 409 \text{ rads/fraction (40 days).*} \end{aligned}$$

B. To calculate the dose per fraction for treatment to be given once per week for six weeks, the formula was applied as follows:

$$\begin{aligned} TD &= NSD \cdot N^{.24} T^{.11} \\ &= 1{,}800 \cdot 6^{0.24} 35^{.11} \\ &= 1{,}800 \cdot 1.53729 \cdot 1.4785 \\ &= 1{,}800 \cdot 2.273 \\ N \cdot d &= 1{,}800 \cdot 2.273 \\ d &= \frac{4{,}091}{6} \\ &= 682 \text{ rads/per fraction.} \end{aligned}$$

From a total of 170 patients who received one or two fractions per week, three categories of cases were selected. These represent the malignant tumors most commonly treated with a reduced number of fractions. Seventy-two patients were deemed suitable for review. The remaining patients were not considered for a variety of reasons including: non-epithelial tumors; mixtures of fractionation schemes including other than one or two fractions per week; or categories of disease too small to allow meaningful conclusions. The response of metastases was evaluated only for the site of origin and regional lymphatics, *e.g.*, response of osseous metastases was not reviewed. Table II indicates the number and category of patients reviewed. No patient was lost to follow-up.

RESULTS

CARCINOMA OF THE BREAST

A total of 26 female patients with adenocarcinoma confined to the breast, or chest wall and regional lymphatics was treated with reduced fractionation. One group of 13 patients had no macroscopic disease (post-

Table II

CATEGORIES OF MALIGNANT DISEASE TREATED WITH REDUCED FRACTIONATION

	Patients
Breast	26
Lung	25
Skin	21
Total	72

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* 405 rads/fraction in 37 days.

TABLE III

CANCER OF BREAST TREATED WITH REDUCED FRACTIONATION

Case	Radiation Energy	Fractions Per/wk.	No. of Fractions Dose/ Fractions	Rads	Rets	Recurrent Disease	Status	Months	Tissue Morbidity
					No Macroscopic Disease				
35 PO*	13e[1]	2	10×400	4,000	1,460	ō	As̄	20	ō
88 PO	13ē	2	10×420	4,200	1,571	ō	As̄	24	Skin telangiectasis
88 PO	13ē	2	11×400	4,400	1,600	ō	As̄	21	ō
61 PO	6 MVX[2]	1	7×600	4,200	1,709	ō	As̄	24	ō
58 PO	13ē	2	19×295	5,605	1,716	ō	Dc̄	18	ō
84 PO	12ē	1	10×480	4,800	1,722	ō	Ds̄	16	ō
63 PO	13ē	2	11×420	4,620	1,728	ō	As̄	35	Telangiectasis
81 PO	12ē	2	19×300	5,700	1,745	ō	As̄	19	ō
81 PO		2	20×300	6,000	1,854	ō	Ds̄	22	ō
47 PO	6 MVX	2	12×400	4,800	1,747	ō	As̄	13	ō
52 PO	25 MVX	2	12×400	4,800	1,747	ō	As̄	22	ō
68 PO	13ē	2	12×400	4,800	1,747	ō	As̄	15	ō
68 PO	13ē	2	12×405	4,860	1,800	ō			
53 PO	13ē	2	15×350	5,250	1,800	ō	As̄	34	Normål, soft ō
62 PO	12ē	2	12×405	4,860	1,800	ō	As̄	14	Skin atrophy+tanning
65 PO	15ē	2	12×506	6,072	2,250	ō	As̄	29	Telangiectasis, atrophy depigmented, severe
					Macroscopic Disease				
63 INOP†	13ē	2	9×420	3,780	1,414	Persistent	Dc̄	1	ō
63	12ē	2	10×420	4,200	1,571	Persistent	Dc̄	2	
55 INOP	15ē	2	13×365	4,745	1,639	ō	Ds̄	16	Skin thickening
71 B‡	15ē	2	11×405	4,455	1,645	ō	As̄	12	Telangiectasis
80	13ē	1	8×550	4,400	1,705	Persistent	Dc̄	4	
85	25 MVX	2	12×400	4,800	1,747	Recurrence 15 mo.	Dc̄	19	
63	6 MVX	2	12×405	4,860	1,781	Recurrence 11 mo.	Ac̄	11	
64	12ē	1	7×620	4,340	1,800	Recurrence 7 mo.	Dc̄	7	
73 INOP	6 MVX	2	12×405	4,860	1,800	13 mo. Persistent	Ac̄	13	Subcutaneous. Normal thickening
52	12ē	1	10×500	5,000	1,836	21 mo.	Dc̄	25	Indeterminate
53	6 MVX	2	20×300	5,856	1,840	ō	As̄	15	ō
78§ (Ref)	13ē	2	8×420 +3×535	4,965	1,950	ō	As̄	35	ō
80 INOP	15ē	2	12×400 +2×500	5,800	2,100	Persistent	Dc̄	6	ō

* PO= Postoperative.
† INOP= Inoperative.
‡ B= Biopsy only.
§ Ref= Refused.
[1] 13 million electron volt electron beam.
[2] 6 million electron volt photon beam.

A= alive.
D= dead.
s̄= without disease.
c̄= with disease.

operative group), while a second group of 13 patients had macroscopic disease (inflammatory carcinoma, locally inoperable or recurrent disease, or refused operation).

Twenty-nine portals were treated with either one or two fractions per week to doses which varied from 1,400–2,300 rets. The majority, however, received 1,700–1,800 rets. In many cases several different portals in the same patient were treated with electrons of similar energy (*i.e.*, multiple chest wall portals plus internal mammary, etc.) and were counted as a single portal. If different energies or sessional doses (one to two times per week) were used in the same patient, the portals are counted separately.

Analysis of the data in Table III indicates that local control of the areas treated prophylactically with one or two fractions per week (no macroscopic disease) was obtained in 16 portals in 13 patients. No evidence of recurrent disease was recorded during the period of observation of 12–35 months (average 19 months).

In the group of 13 patients with macro-

Table IV

SKIN AND SUBCUTANEOUS TISSUE MORBIDITY

Rets	Tanning	Telangiectasia	Thickening	Atrophy	Depigmented Skin
1,460	*				
1,571		*			
1,639			*		
1,728		*			
1,800			*		
1,800				*	
2,250	†	‡	‡	‡	‡

* Minimal.
† Moderate.
‡ Severe.

scopic disease there were four inoperable cases; two died with disease before six months, one died at 16 months without disease and one patient is living with persistent disease at 13 months. A fifth patient refused surgery (although operable) and received irradiation alone and is alive without disease at 35 months. The ret dose in this case reached 1,950. A sixth patient had biopsy only of breast and axilla and was treated with irradiation alone and is alive without disease at twelve months (1,645 rets).

Of the remaining seven patients in this group, five have died with uncontrolled local disease after two, four, seven, 15 and 25 months. One patient is alive with disease at eleven months and one patient is alive without disease after 15 months. Local control was obtained during the period of observation or until death in four of this group of 13 patients.

Table iv relates the skin and subcutaneous reactions resulting from one and two fractions per week to the ret dose. The immediate skin reactions were not tabulated for the doses and fractions utilized, however most were fairly severe with marked erythema and spotty desquamation being common when ret doses reached 1,700–1,800. Skin sparing was deliberately avoided and bolus was utilized with 6–25 MeV photons. Electron beams have a minimal "skin sparing," but it is extremely difficult to measure this small differential at the surface.

CARCINOMA OF THE SKIN

Analysis of the treatment received by 21 patients with carcinoma of the skin, utilizing one or two fractions per week, is shown in Table v. Three recurrences were noted, all within one year. The median duration of observation following treatment is 29 months. Table vi relates the short term morbidity for normal tissues to the ret dose. With one or two fractions per week, moderate changes are found at all dose levels, but little correlation with increasing ret doses between 1,781 and 2,140 rets is seen.

CARCINOMA OF THE LUNG

Table viiA presents the data for treatment of 15 patients with carcinoma of the lung with "curative intent," using one or two fractions per week. Table viiB presents similar data for patients treated with "palliative intent." Patients with disease confined to the thorax were treated with "curative intent" while those who had distant metastasis were treated with "palliative intent," and only the thoracic response was evaluated. Only five of the 16 patients living four or more months had complete disappearance of the treated primary tumor. Of these, four, and possibly five, recurred before death.

TABLE V

CANCER OF THE SKIN TREATED WITH 1–2 FRACTIONS PER WEEK

E[1]	Fractions Per/wk.	No. of Fractions Dose/Fractions	Total Dose Rads‡	Rets	Months at Recurrence	Site of Lesion	Months Follow-Up
170 KV	1	7×500	3,500	1,512	12	ear	27 As̄*
280 KV	1	5×646	3,230	1,610	0̄		29 As̄
120 KV	1	7×520	3,640	1,612	0̄		32 As̄
280 KV	2	6×387					
			4,202	1,662§	0̄		34 As̄
	1	5×376					
120 KV	1	6×610	3,660	1,764	0̄		28 As̄
6 MEVē	1	6×680	4,080	1,781	0̄		29 As̄
170 KV	1	6×612	3,672	1,781	0̄		30 As̄
170 KV	1	6×612	3,672	1,781	0̄		33 As̄
120 KV	1	6×612	3,672	1,781	0̄		24 As̄
120 KV	1	6×612	3,672	1,781	0̄		24 As̄
170 KV	2	12×364	4,374	1,795	0̄		10 As̄
120 KV	1	6×615	3,690	1,797	0̄		32 As̄
170 KV	1	6×614	3,684	1,797	2	nose	8 Ac̄†
120 KV	2	6×567	3,402	1,800	0̄		29 As̄
120 KV	1	7×558	3,906	1,800	0̄		25 As̄
170 KV	2	11×400	4,400	1,892	0̄		40 As̄
170 KV	2	11×400	4,400	1,892	0̄		33 As̄
120 KV	1	6×648	3,888	1,947	0̄		29 As̄
170 KV	1	6×648	3,888	1,947	0̄		34 As̄
170 KV	1	7×612	4,284	2,036	0̄		10 As̄
120 KV	1	4×880	3,520	2,096	0̄		34 As̄
25 MEVē	1	6×690	4,140	2,140	5	ear	25 As̄

* As̄= Alive without disease.

† Ac̄= Alive with disease.

‡= The dose/fraction and total dose in rads, as shown in the table, must be corrected by the R.B.E. of 0.9 for 60 Co before calculating the ret dose by the Ellis formula.

§= Partial tolerances and recovery factors used to calculate ret dose.

[1]= KV= kilovoltage.

MEVē= million electron volt electron beam.

DISCUSSION

CARCINOMA OF THE BREAST

The ret doses given for postoperative irradiation following mastectomy have generally approached full tolerance and represent a higher ret dose than the usual practice of giving 25 fractions of 200 rads treating five times per week. This latter scheme, calculated in accordance with the Ellis formula[2,3] for partial tolerance, is equivalent to 1,450 rets. Fletcher[5] advocates giving 20 fractions of 250 rads treating five times per week. This results in a ret dose of 1,636, and is stated to prevent local chest wall recurrences in 90 percent of patients[10] and freedom from disease in peripheral lymphatics in 98 percent of patients.[6] While the numbers are small, there have been no chest wall recurrences in our group of 13 postoperative patients, although we treated to a higher ret dose in all but three patients. The acute reactions were not tabulated but generally were moderately severe with marked erythema and spotty desquamation (Fig. 1). The acute reactions were expected in all patients since bolus was used to avoid skin sparing with photon beams. The late reactions seem satisfactory for this brief period of observation (Fig. 2).

The second group of 13 patients all had macroscopic disease. The ret doses achieved varied between 1,414–2,100 with a mean of

TABLE VI

ANALYSIS OF TISSUE CHANGES—1–2 FRACTIONS PER WEEK

Site	No. Fractions Dose/Fractions Fractions per/wk.	Rets§	Months	Telangiectasis	Atrophy	Subcutaneous Fibrosis	Depigmented
Helix-R	7×500/1	1,512	12	*	*	0̄	*
Helix-L	5×646/1	1,610	29	0̄	*	0̄	*
Tip-Nose	7×520/1	1,612	22	—1	—	—	—
Helix-L	6×387/2 5×376/1	1,662	32	*	*	0̄	*
Lip-Upper	6×610/1	1,764	28	—2	—	—	—
Tip-Nose	6×680/1	1,781	29	0̄	0̄	0̄	*
Tip-Nose	6×612/1	1,781	23	0̄	0̄	0̄	0̄
Cheek	6×612/1	1,781	30	0̄	0̄	0̄	*
Eyelid-Lower	6×612/1	1,781	33	*	†	0̄	*
Ear-L	6×612/1	1,781	24	*	† cartilage	0̄	*
Helix-L	12×364/2	1,795	10	0̄	*	0̄	*
Nose	6×615/1	1,797	32	0̄	†	0̄	†
Nose-Bridge	6×614/1	1,797	8	0̄	*	0̄	
Cheek	7×558/1	1,800	25	—3	—	—	—
Cheek-R	6×567/1	1,800	29	0̄	‡	0̄	‡
Naso-orbital	11×400/2	1,892	33	*	*	0̄	†
Cheek-L	11×400/2	1,892	40	*	*	0̄	†
Ala-Nose	6×648/1	1,947	34	0̄	*	0̄	*
Tip-Nose	6×648/1	1,947	29	0̄	*	0̄	*
Eyelid Lower-R	7×612/1	2,036	10	*	*		*
Naso-labial-R	4×880/1	2,096	34	0̄	*	0̄	*
Ear-L	6×690/1	2,140	5	0̄	†	0̄	*

*= Minimal.
†= Moderate.
‡= Severe.
§= The dose/fraction and total dose in rads, as shown in the table, must be corrected by the R.B.E. of 0.9 for 60 Co before calculating the ret dose by the Ellis formula.
1, 2, 3= Patient seen in follow-up only by private physician.

1,756 which compares to the mean of 1,750 for the microscopic disease group. So far as can be determined, the acute and short term soft tissue morbidity is comparable between the two groups. Local control was achieved in three of six patients treated with the breast intact and only one of seven treated for postoperative recurrence.

The patient material is too small to draw any meaningful conclusions. We have established that reduced fractionation schemes are well tolerated by the patient. The acute and short term morbidity is not excessive and further trials with reduced fractionation schemes seem warranted.

CANCER OF THE SKIN

There are few areas in which radiotherapists are more confident of their ability to cure cancer than that of the skin. Published series[4] over the past 50 years have attested to the excellent cure rates in excess of 90 percent, attained with a wide variety of dose-time-fractionation schemes. The classical work of Strandqvist[9] in 1944 based on 280 cases of carcinoma of the skin and lip constituted the first quantitation of dose-time factors derived from clinical observation, and his curves have been utilized as a valuable predictive guide to clinical treatment. That carcinoma of the skin constitutes a readily available human model is obvious and much basic and fundamental knowledge concerning malignant cell response, skin tolerance, erythema, and necrosis has been gained from clinical ob-

TABLE VIIA

CANCER OF THE LUNG ANALYSIS OF 1 AND 2 FRACTIONS PER WEEK

(Curative Intent)*

Age/Sex	Fractions per wk.	No. of Fractions Dose/ Fractions	Rads	Rets	Tumor Regression	Lived Months	Recurrent Growth of Tumor Locally
64 F	2	6×405	2,430	890	Incomplete	1 Dc̄	Persistent
53 M	2	8×405	3,240	1,188	Indeterminate	3 Dc̄	0̄
76 M	1	8×500	4,000	1,468	Incomplete	6 Ds̄	4 months
47 M	2	12×400	4,800	1,747	Incomplete	5 Dc̄	0̄
66 M	2	10×450	4,500	1,751	Incomplete	3 Dc̄	0̄
65 M	2	10×455	4,550	1,781	Indeterminate	4 Dc̄	0̄
50 M	2	12×405	4,860	1,781	Incomplete	12 Dc̄	0̄
53 M	2	10×455	4,550	1,781	Complete	7 Dc̄	4 months
75 M	1	6×680	4,080	1,781	Complete	7 Dc̄	6 months
66 F	2	20×300	6,000	1,785	Complete	35 Ac̄	Questionable at 35 months
80 M	2	3×300 5×320 6×400	5,150	1,795	Incomplete	4 Dc̄	
50 M	1	7×630	4,410	1,844	Complete	5 Dc̄	4 months
72 M	2	13×400	5,200	1,892	Incomplete	8 Dc̄	0̄
53 M	1	9×550	4,950	1,918	Incomplete	6 Dc̄	0̄
61 M	2	11×450	4,950	1,926	Complete	3 Dc̄	0̄

TABLE VIIB

(Palliative Intent)†

73 M	1	7×250 (whole lung)	1,750	434	Incomplete	3 Dc̄	
71 M	2	8×300	2,400	742	Incomplete	2 Dc̄	
66 M	2	7×405	2,835	1,039	Incomplete	8 Dc̄	
83 M	2	10×400	4,000	1,456	Indeterminate	3 Dc̄	
64 F	1	6×620	3,720	1,542	Complete	4 Dc̄	
64 F	1	6×620	3,720	1,542	Complete	2 Dc̄	
57 M	1	10×455	4,550	1,580	Incomplete	6 Dc̄	
75 M	1	6×680	4,080	1,781	Incomplete	5 Dc̄	
80 F	2	12×408	4,896	1,802	Incomplete	2 Dc̄	
65 F	1	7×250 7×630 (whole lung)	1,750 4,410	434 1,844	Incomplete	5 Dc̄	

*= Curative Intent—no disease beyond thorax.
†= Palliative Intent—thoracic disease treated but metastases present.
Dc= Dead with disease.
Ds= Dead without disease.
Ac= Alive with disease.

servation of irradiated patients. This information has been applied to the treatment of malignancies at other sites and in large part accounts for the conventional 6,000 rads in six weeks given at the rate of 180–200 rads per fraction five times per week. It is the response of normal skin and skin cancer to radiation as documented by Strandqvist,[9] Cohen,[1] Fowler,[7] Jolles and Mitchell[8] and others that is the basis for the formula derived by Ellis. The philosophy underlying the formula has been discussed in numerous publications and will not be repeated here. This review of skin cancers treated by one or two fractions per week is of importance in testing the predictive value of the formula and is likely to be applicable to sites other than the skin. A review of Table v indicates that 22 carcinomas of the skin were treated, the majority of which were basal cell carcinomas (16) and the remainder squamous cell carcinomas (six). As is true in most departments, the location is principally the skin of the face and predominantly the nose, ears and eyelids. With the exception of three cases which were recurrent from previous treatment other than radiation, all were primary lesions.

Of 22 lesions treated, there have been three recurrences during the observation period of 5–40 months. Two recurrences, one at twelve months and the other at five months involved relatively large lesions of the ear. The third patient had a large lesion of the nose with a small persistent area of disease after irradiation which was removed surgically. The remaining 18 cases, treated predominantly with one fraction, and to a lesser extent two fractions per week, in the range of 1,700–1,900 rets, have remained controlled ten to 40 months (median 29 months).

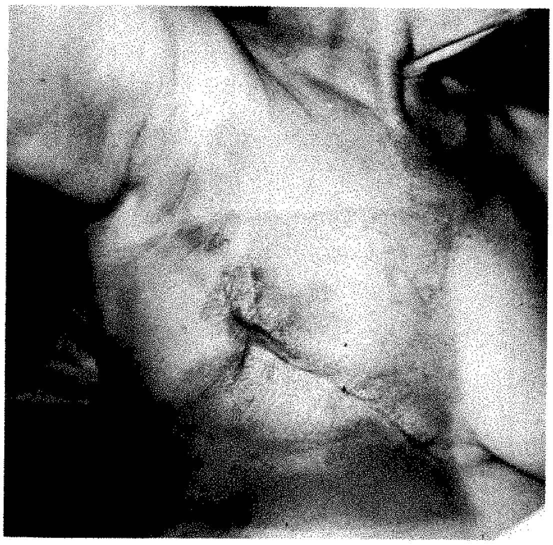

FIG. 1. Chest wall postoperative. Fifteen fractions times 350 rads two times per week (4,860 rads–1,800 rets) using 13 MeV electron beam, 20×20 cm field size at 200 cm S.T.D. Photograph taken at time of last treatment.

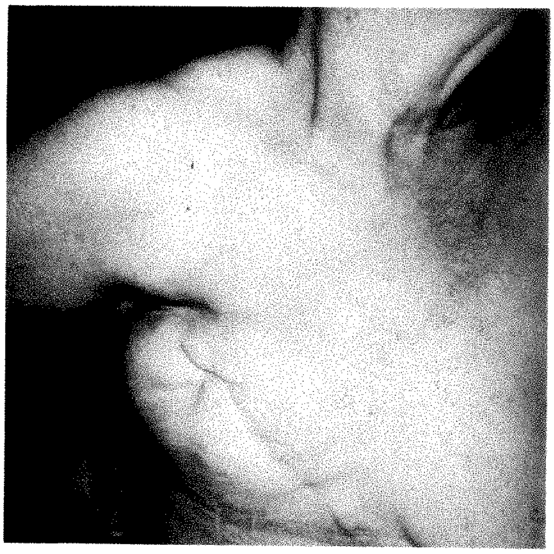

FIG. 2. Same patient as Figure 1. Photograph taken two years after last radiation treatment.

The aesthetic result of one or two fractions is of importance in view of the long held belief that protraction is necessary to achieve cure while producing minimal skin changes such as atrophy, depigmentation and telangiectasis or subcutaneous fibrosis. Of the 22 lesions treated, three patients could not be followed directly in our department and skin changes were not reported for these patients in Table vi. These patients, however, are all reported to be alive and free of cancer by their family physicians. Of the remaining 18 lesions, the majority showed minimal atrophy and depigmentation with few cases showing telangiectases (Fig. 3–5). Only one patient was scored as having severe changes with both atrophy and marked depigmentation. Four patients showed moderate atrophy and three patients had moderate depigmentation. Subcutaneous fibrosis was absent in all patients (Table viii). These changes do not appear to correlate well with ret doses between 1,500–2,100. While the majority of patients showed some sequelae with one or two fractions per week, these did not seem to be prohibitive or substantially different than usually obtained with more conventional fractionation. The recurrence or persistence of dis-

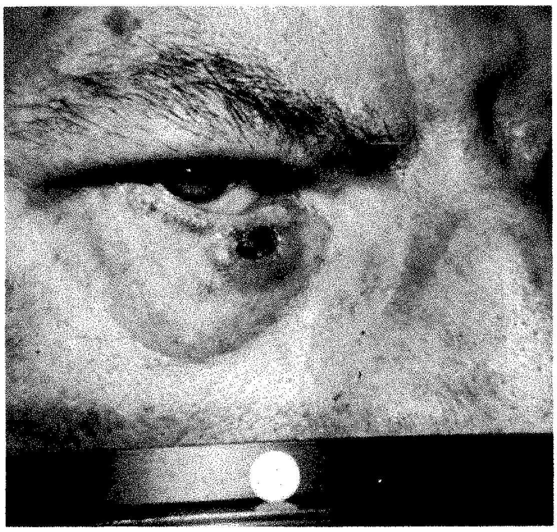

Fig. 3. Pretreatment photograph. Basal cell carcinoma treated with 170 KV. HVL .5 mm copper S.T.D., 37.5 cm. Seven fractions times 612 rads given one time per week. (4,284 rads–2,036 rets) Gap of 21 days between sixth and seventh fractions plus initial fraction 605 rads rather than 612 rads.

ease in three of the 22 lesions treated is of interest but firm conclusions must be deferred until further follow-up is available and a larger number of cases has been analyzed. Similarly, full analysis of late morbidity must await a longer period of observation after treatment. The eventual application of this information to the treatment of carcinomas arising in other sites may be possible as has been true from experience with carcinoma of the skin from the earliest days of radiation therapy.

CANCER OF THE LUNG

Twenty-five patients with carcinoma of the lung were treated using one or two fractions per week and this departure from conventional fractionation seems justifiable in view of the generally poor curative results obtained regardless of the manner in which irradiation is given. Despite every effort at more vigorous local control, cure rates remain largely unchanged due to rapid dissemination of disease outside of the treated area, but failure of local control still remains a significant factor.

Fifteen patients were treated with curative intent (Table viiA) *i.e.*, these patients were considered to be technically inoperable or were medically unsuitable for curative surgical procedures due to complicating chronic obstructive pulmonary disease and other medical problems. The entire known tumor volume and its complex of spread were treated using six or 25 million volt photon beams and a dosage of 1,800–1,900 rets. Of these 15 patients treated with one or two fractions per week, one is alive with disease at 34 months, and a second survived for twelve months. A third patient died of intercurrent disease at four months. The remaining twelve patients followed the characteristically dismal survival with this disease and have died at or shortly after one to eight months.

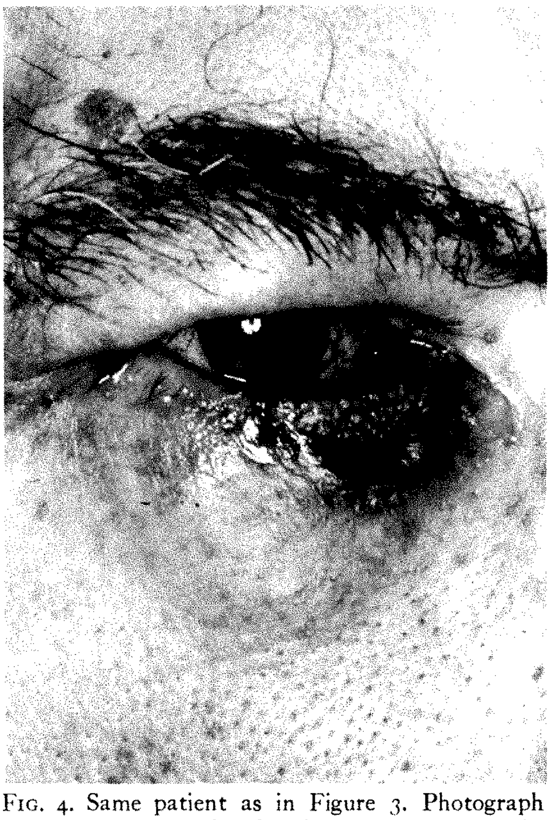

Fig. 4. Same patient as in Figure 3. Photograph taken one week after fourth treatment, ten weeks after Figure 3.

The tumor response appeared to be complete (*i.e.*, regression) in five cases and partial in seven cases. Thus, twelve of the 15 patients showed a tumor response. It is of interest that of the four cases treated with one fraction per week, all showed a response (two complete, two incomplete) but none survived appreciably beyond six months. One of these cases had no identifiable disease at postmortem examination although the ret dose was less than 1,500.

The one lone survivor (alive 34 months) was treated with a total ret dose of 1,785. Morbidity from one or two fractions per week was absent except for occasional dysphagia. No patient is noted to have had any untoward symptoms of dyspnea, pain or hemoptysis, nor any objective pneumonitis or pericarditis. Symptoms were relieved or improved in two-thirds of the patients.

A second group of ten patients with distant metastases was considered suitable for palliative radiation only to relieve symptoms resulting from the primary tumor (Table VIIB).

The results in this small group treated palliatively are also as expected. All were dead either before or slightly after the six month period. Two of the ten patients showed a complete regression of the tumor while seven had some response. Morbidity was minimal or absent but the ret doses were slightly less than in the curative group. Symptoms were improved temporarily in the majority of patients, many with superior vena caval obstructive symptoms.

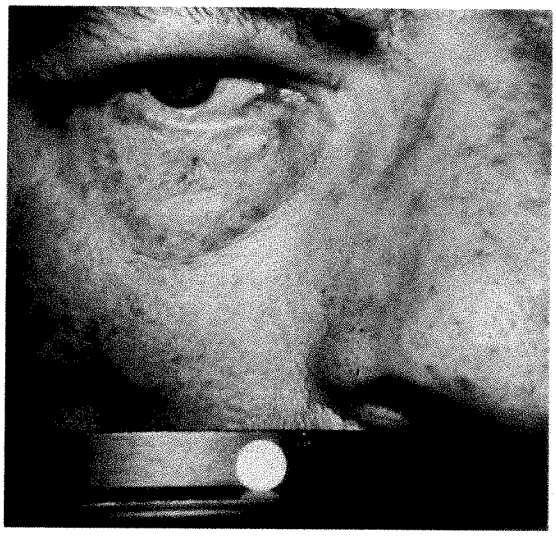

FIG. 5. Same patient as in Figure 3. Photograph taken seven months after treatment.

It would seem that treatment of cancer of the lung with one or two large fractions per week is not substantially different from conventional fractionation with regard to local tumor control, and immediate morbidity.

CONCLUSIONS

Short term tumor control with one or two fractions per week is not substantially different than would be expected, site for site, from the available literature utilizing more conventional fractionation, although ultimate tumor control is not yet evaluable.

The acute reactions, both local and systemic, to large fractional doses do not seem to be prohibitive.

The period of observation is too brief to

TABLE VIII

SKIN CHANGES AS RECORDED IN TABLE VI

Degree of Change	Telangiectasis	Atrophy	Depigmentation	Subcutaneous Fibrosis
Minimal*	7	11	13	0
Moderate†	0	4	3	0
Severe‡	0	1	1	0
Total	7	16	17	0

permit more than tentative conclusions concerning the late morbidity for which the NSD concept is designed to be predictive.

Additional prospective trials to test the validity of the formula as a guide to clinical practice are needed.

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PATTERNS OF FAILURE IN INTRACRANIAL ASTROCYTOMAS AFTER IRRADIATION: ANALYSIS OF DOSE AND FIELD FACTORS*

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ABSTRACT:

The choice of tumor dose and treatment volume are the two most important radiation factors influencing survival in glioblastomas. Patients treated to their whole brain survive longer than those treated with limited fields. Glioblastomas treated with over 5,000 rads (1,300 rets) survive longer than those treated with smaller doses. Other factors affecting survival are: the pathological grade; age at diagnosis; and surgical treatment performed. Failure patterns in glioblastomas represent intrinsic qualities of the tumor, the host, and the treatment employed. They dictate the strategy to follow. Perhaps some of these are unaffected by irradiation. An increase in dose and the extension of fields in glioblastomas have produced a gain in both the quantity and the quality of survival. The whole brain is treated (5,000–6,000 rads) and the target volume is boosted to 7,000 to 8,000 rads. Grade II astrocytomas perhaps should be treated with whole brain irradiation (4,500 rads) and a boost to the target volume of an additional 1,000 rads.

THE two most important radiotherapeutic factors in the survival of intracranial astrocytomas are the choice of tumor dose and the extension of treatment fields beyond the locus of involvement. Almost 50 percent of all primary brain neoplasms are astrocytomas;[5,6,15,19,39,41,54] in childhood, when brain tumors rank second only to leukemia in frequency,[21,51,52] these tumors become even more worthy of remark. There has been, with the unique exception of Grade I cerebellar tumors, a significant gain in survival with the addition of radiation therapy postsurgically (Table I). The over-all five year survival is nevertheless perhaps the worst of the common primary brain tumors. The issue is whether the quantity and the quality of survival can be improved by a careful manipulation of treatment factors.

The extension of fields and the dose selection are a function of the patterns of failure as seen in our experience and in the literature. The rapid spread and anoxic component of these tumors become essential considerations in their management. The combination of whole brain and high dose irradiation is seen to yield the best results in glioblastomas. Grade II astrocytomas will probably require lower doses and whole brain irradiation. A relatively large series of cases treated with different philosophies over 15 years permits comparison and indicates the strategy to follow.

MATERIAL AND METHOD

A review of the records from January 1, 1960, to March 1, 1975, at the Radiation Oncology Department of the University of Rochester* yielded 148 cases of primary brain astrocytomas. The follow-up was

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* Thirty cases from the Radiation Therapy Department of the University of Puerto Rico with complete follow-up were included through the courtesy of Victor A. Marcial, M.D.

* Presented at the Fifty-seventh Annual Meeting of the American Radium Society, Isla Verde, Puerto Rico, May 4–9, 1975.

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† Division of Neurosurgery, Strong Memorial Hospital.

‡ Division of Biostatistics, University of Rochester.

TABLE I

SURVIVAL OF INTRACRANIAL ASTROCYTOMAS BY PATHOLOGICAL GRADE AND TREATMENT: A REVIEW OF THE LITERATURE EXCLUDING THE PRESENT SERIES

Tumor Type	Treatment Type*	Percent Survival†					Reference Number(s)
		1 yr.	2 yr.	3 yr.	4 yr.	5 yr.	
Grades I, II	S	60–81	—	52–64	—	26–64	32,47
	S+RT	58–86	—	31–64	—	26–50	6,32,43,46,47
Grade I	S	—	—	—	—	76	32
	S+RT	64–90	—	36–86	—	86	6,22,43
Grade II	S	—	—	—	—	—	—
	S+RT	50	33	16–25	17	—	22,43
Grades III, IV	S	0–10	0–5	0–3	0	0	14,45,46
	S+RT	20–44	8–23	0–16	0–10	0–9	2,6,14,20,28,41,43,45–47
Grade III	S	—	—	7	—	3	47
	S+RT	60	—	14–27	10	0–16	22,43,47
Grade IV	S	—	—	0	0	0	47
	S+RT	30–32	0–7	0–6	0–2	0–2	22,41,43,47

* S= Surgical; S+RT= Surgery+Postoperative Irradiation.

† Percent survival given as minimum values to maximum values reported for series.

complete in all cases. Survival was estimated from the time of pathological diagnosis.

GENERAL FACTORS

The age and sex distribution and the localization within the cerebrum of the cases are presented in Figures 1 and 2. Pathological material was available for review in all cases except five; in these the pathology report was utilized. All cases reviewed at our Pathology Department were graded from I to IV following Kernohan and Sayre's[22] classification. Only seven cases (five percent) were Grade I, since these tumors are mostly cystic, completely excised, and seldom referred for postoperative irradiation treatment. Thirty-seven (25 percent) were Grade II, 50 (34 percent) Grade III, and 54 (36 percent) Grade IV tumors.

STATISTICAL CONSIDERATIONS

The graphs presented in this report depict the survival experience of the individuals in the study for various combinations of factors influencing survival. These survival plots were obtained using the method of Kaplan and Meier[21] and illustrate the probability of survival on a natural logarithm scale as a function of time (in months). While the points on each graph have been joined with straight lines, it would be more correct, but less illuminating, to construct step functions with the plotted points as left-end points of each step. If such a plot (on a logarithmic scale) appears linear, then we have evidence of exponential survival.[53] The magnitude of the slope of the line is an estimate of the (constant) failure rate of the group of individuals in question.

Two such failure rates, λ_1 and λ_2, can be compared by noting that the quantity

$$\frac{V_1/r_1}{V_2/r_2}\left(\frac{\lambda_1}{\lambda_2}\right)$$

follows an F distribution with $2r_1$ and $2r_2$ degrees of freedom, where r_i is the number of deaths in group i, $i=1, 2$ and Vi is the sum of all the observations (deaths and censored) in the ith group. The above mentioned statistic enables one to place a confidence interval on the ratio of the two failure rates. If the confidence interval includes the point of unity, then there is evidence of equal failure rates. If, however, the confidence interval lies entirely to the right (left) of unity, then λ_1 (λ_2) will be statistically larger (smaller) than λ_2 (λ_1) at the chosen level of confidence. Comparisons of the appropriate failure rates together with estimated probabilities of survival of one through five years inclusive appear in the Tables of this report.

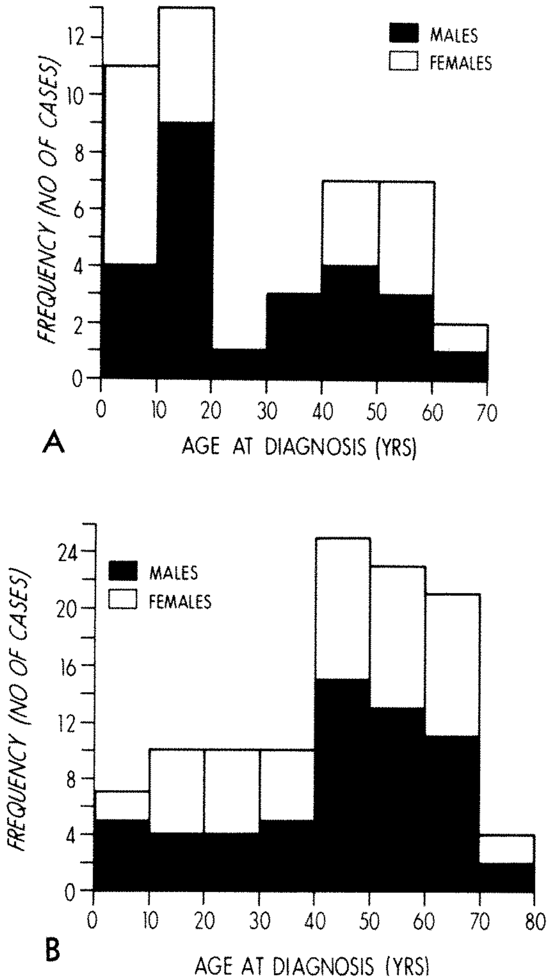

FIG. 1. (*A*) Age and sex distribution of 44 intracranial astrocytomas, Grades I and II. (*B*) Age and sex distribution of 104 intracranial astrocytomas, Grades III and IV (glioblastoma multiforme).

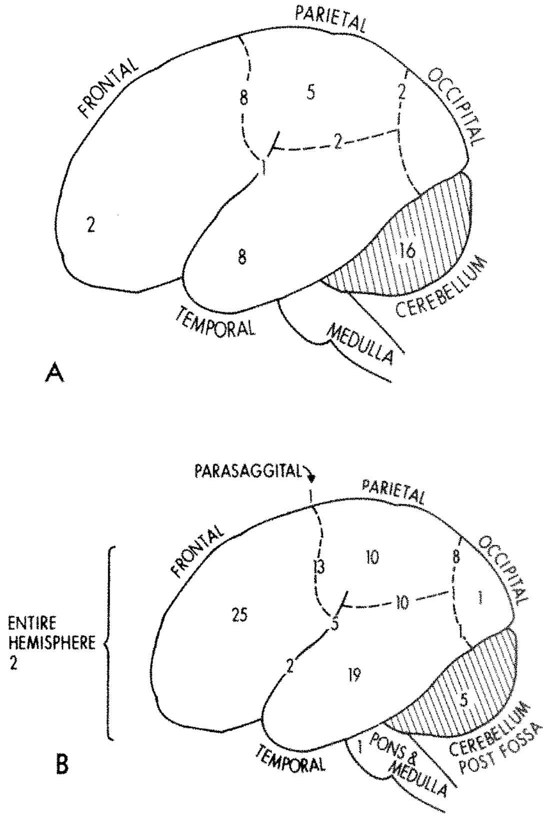

FIG. 2. (*A*) Location of 44 intracranial astrocytomas Grades I and II (17 right side, 19 left side, and eight midline). (*B*) Location of 104 intracranial astrocytomas Grades III and IV (glioblastoma multiforme).

SURGICAL TREATMENT

All 148 patients had surgical treatment prior to radiation therapy. In only 18 was the tumor totally resected; it was partially removed in the remaining 130 (88 percent). All tumors in this series, except one, were subjected to postoperative irradiation treatments with megavoltage photon teletherapy at distances of 88 cm or more. Fourteen patients (ten percent) did not complete irradiation treatments and received less than 1,000 rets. Although these 14 cases, plus the one treated by surgery alone, constitute surgical failures, they have been kept in the study for purposes of comparison. Patients who completed irradiation treatments and did not survive one or two

TABLE II

EFFECT OF TREATMENT ON THE PERFORMANCE STATUS IN 148 INTRACRANIAL ASTROCYTOMAS

Change in Percent Performance Status*	Percent of Grades I–II Patients		Percent of Grades III–IV Patients	
	Postop.	Post-RT	Postop.	Post-RT
	(44)†	(44)	(104)	(89)‡
≥ 30 percent	5	16	0	5
Better by ≥ 20 percent	7	32	6	30
≥ 10 percent	16	28	14	28
No Change	32	18	19	22
≥ 10 percent	23	2	34	12
Worse by ≥ 20 percent	11	5	13	2
≥ 30 percent	7	0	13	0

* Karnofsky Performance Status: 100 percent = Normal, asymptomatic, NED; 90 percent = Normal actions, minor signs and symptoms of disease; 80 percent = Normal actions with effort, some signs and symptoms of disease; 70 percent = Self-care, unable to carry on normal actions; 60 percent = Requires occasional assistance, care for most of his needs; 50 percent = Requires considerable assistance, frequent medical care; 40 percent = Disabled, requires special care and assistance; 30 percent = Severely disabled, hospitalization indicated, death not imminent; 20 percent = Very sick, hospitalization and active support treatment necessary; 10 percent = Moribund, fatal process progresses rapidly; 0 percent = death.

† Postop. = Postoperatively; Post-RT = After completion of radiation therapy; numbers in parentheses represent the total number of patients in each category.

‡ Fifteen patients did not complete a full course of radiation therapy.

TABLE III

SURVIVAL OF 148 INTRACRANIAL ASTROCYTOMAS: EFFECT OF AGE, TYPE OF SURGERY, AND PATHOLOGY

Facts Influencing Survival	Categories	Time Failure Rate and Its Estimate (Months)$^{-1}$	Estimated Percent Surviving					Statistical Significance	90 Percent Confidence Interval(s) for Ratio(s) of True Failure Rates
			1 yr.	2 yr.	3 yr.	4 yr.	5 yr.		
Age (yr.)	≤30, I–II	λ_1, 0.0035	96	92	88	85	81	>+	$3.13 \le \frac{\lambda_2}{\lambda_1} \le 16.67$
and	≤30, III–IV	λ_2, 0.0230	76	58	44	33	25		
	>30, I–II	λ_3, 0.0319	68	47	32	22	15	>+	$1.18 \le \frac{\lambda_4}{\lambda_3} \le 2.94$
Grade	>30, III–IV	λ_4, 0.585	50	26	12	6	3		
Surgery	Total, III–IV	λ_1, 0.0217	77	59	46	35	27	>+	$1.35 \le \frac{\lambda_2}{\lambda_1} \le 5.00$
and	Partial, III–IV	λ_2, 0.0517	54	29	16	8	5		
Grade	Total, I–II*	λ_3, —	—	—	—	—	—		
	Partial, I–II	λ_4, 0.0124	86	74	64	55	48		
	Grade I†	λ_1, —	—	—	—	—	—		
Grade	Grade II	λ_2, 0.0103	88	78	69	61	54	>+	$2.00 \le \frac{\lambda_3}{\lambda_2} \le 5.56$
	Grade III	λ_3, 0.0336	67	45	30	20	13	>+	$1.35 \le \frac{\lambda_4}{\lambda_3} \lesseqgtr 3.00$
	Grade IV	λ_4, 0.0676	44	20	9	4	2		

* Estimates for this group are not available because all schedules in the group are censored. The actual censored times in months are as follows: 6, 16, 36, 48, 60, 63, 74.

† Estimates for this group are not reliable because the data consist of only seven observations, three failures at 3, 12, and 12 months, and four censored at 15, 60, 60, and 120 months.

months have not been excluded nor considered surgical failures in this report.

IRRADIATION TREATMENT

Patients with intracranial astrocytomas, with the exceptions mentioned earlier, received doses in excess of 5,000 rads in six and one-half weeks; however, since our cases were from two separate institutions and were collected over a span of 15 years, N.S.D. standardization was utilized according to Ellis'[11] formula.

Low grade astrocytomas, as a rule, were not treated with whole brain irradiation. The irradiated area basically paralleled the tumor bed with adequate margins. The few cases that were treated with larger brain areas had diffuse and extensive disease after surgery.

Glioblastomas (Grades III and IV) were treated at random with partial or whole brain irradiation. The whole brain field, in most cases, encompassed the entire cranial contents, including the middle cranial fossa, by utilizing a line connecting the mastoid tip with the inferior orbital rim (and eye shield) as the inferior limit. As a rule, glioblastomas were treated with doses of 5,000 to 6,000 rads in five to eight weeks with the exception of a recent group of 14 patients who received an additional boost dose to the target volume (the area occupied by the tumor with at least a 2 cm margin). The boost target area received maximum doses of 7,000 to 8,000 rads. This special group of patients, although included in the high grade tumors in this article, constitutes the topic of a separate report.[40]

FAILURES AND QUALITY OF SURVIVAL

There were 105 deaths (71 percent) among the 148 patients. Only 16 (15 percent) had autopsies. The remaining patients were assessed as dying from recurrent disease by either clinical symptoms or roentgenological or scanning findings of tumor recurrences.

The quality of survival was determined retrospectively for all patients using the Karnofsky scale to compare performance status before and after surgery and at completion of radiation therapy (Table II).

PATH. (GRADE)	HIGH (III & IV)		LOW (I & II)	
SURGERY	TOTAL	PARTIAL	TOTAL	PARTIAL
NO. PTS.	11	92	7	37
NO. DEATHS	7	78	0	20

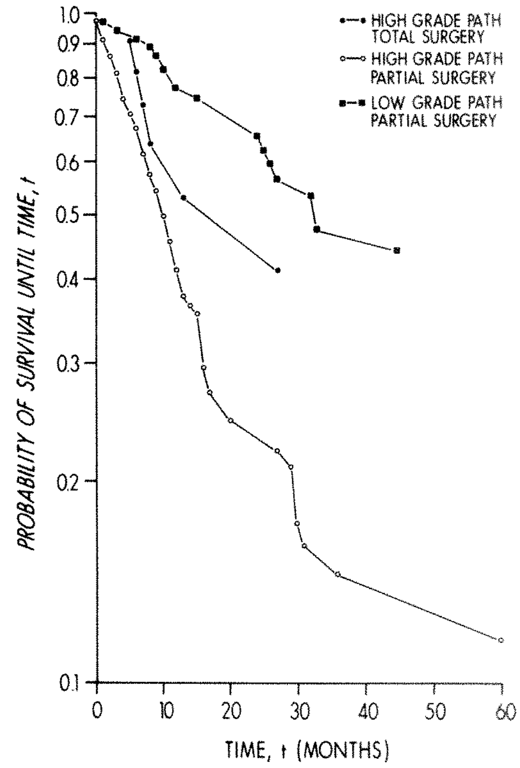

Fig. 3. Failure rate trend of 148 intracranial astrocytomas according to the amount of surgery performed and the pathological grade.

RESULTS

EFFECT OF TREATMENT ON SURVIVAL

Only surgery and radiation therapy were utilized in the treatment of these patients. In our experience, both were relevant to survival.

Surgery Evaluation: An attempt was made to separate patients into groups based on the amount of surgery performed (total or partial) and the pathological grading of their tumors. The results appear in Figure 3 and Table III. The estimates for the group containing completely excised low grade tumors are not available because

TABLE IV

SURVIVAL OF 104 GLIOBLASTOMAS: EFFECT OF DOSE, FRACTIONATION, AND FIELD SIZE

Categories*	Time Failure Rate and Its Estimate (Months)$^{-1}$	Estimated Percent Surviving 1 yr.	2 yr.	3 yr.	4 yr.	5 yr.	Statistical Significance	90 Percent Confidence Interval(s) for Ratio(s) of True Failure Rates
$\le$1300, $\le$200 cm^2	λ_1, 0.1633	14	2	0	0	0	0	$0.76 \le \frac{\lambda_2}{\lambda_1} \le 3.33$
$\le$1300, $>$200 cm^2	λ_2, 0.2500	5	0	0	0	0		
$>$1300, $\le$200 cm^2	λ_3, 0.0628	47	22	10	5	2	+	$1.38 \le \frac{\lambda_3}{\lambda_4} \le 3.27$
$>$1300, $>$200 cm^2	λ_4, 0.0285	71	50	36	25	18		

* Dose given in N.S.D. rets: 1,300 rets is the minimal dose (approximately, 4,500 rads). Irradiated brain areas given in cm^2: 200 cm^2 stands for minimal area to encompass the whole brain.

all seven individuals are alive at 6, 16, 36, 48, 60, 63, and 74 months since diagnosis. A statistical difference was observed when total *versus* partial surgery was compared among Grades III and IV. Patients who had their tumors totally excised lived longer.

Radiation Therapy Evaluation: Among radiation treatment factors influencing survival of intracranial astrocytomas, dose selection, fractionation, and field size yielded important results. These factors are analyzed only for glioblastomas because low grade astrocytomas were generally treated postoperatively with partial brain irradiation (5,000 rads in six and one-half weeks, five fractions per week) and consequently we were unable to establish a comparison.

TARGET VOL. DOSE (RETS)	$\le$1300 RETS		$>$1300 RETS	
IRR. BRAIN AREA (cm^2)	$\le$200 cm^2	$>$200 cm^2	$\le$200 cm^2	$>$200 cm^2
NO. OF PTS.	8	15	24	57
NO. OF DEATHS	8	15	23	39

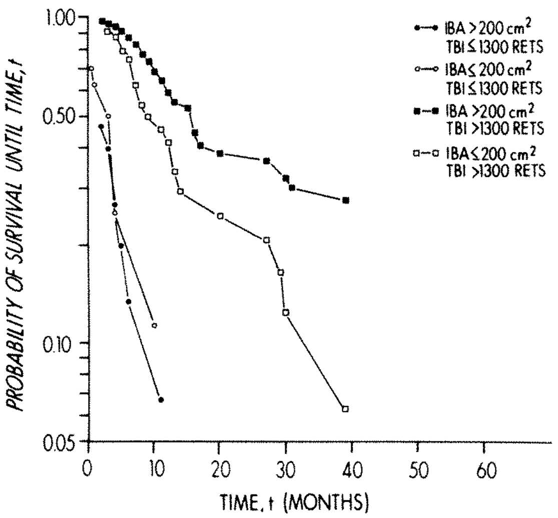

FIG. 4. Failure rate trend of 104 glioblastomas according to dose, irradiated area, and pathology.

If glioblastomas are divided into two categories, those who received doses above and below 1,300 rets (minimal dose around 5,000 rads) and those who were irradiated over or under 200 cm^2 (minimal average area to represent whole brain irradiation), a statistically significant difference is found for each group individually. The results presented in Figure 4 and Table IV were obtained from the combination of these factors. There was no significant difference among the patients treated below minimum doses as far as irradiated brain areas are concerned, because of the effect of dose for these patients. When the patients receiving adequate doses (over 1,300 rets) are compared with regard to partial or whole brain irradiation, a striking difference is noted; the best results were observed in patients treated with doses in excess of 1,300 rets and whole brain irradiation.

PATTERNS OF FAILURE

The patterns of failure for the entire series is presented in Table V. Although the majority of the failures were within treated brain areas, a significant number of failures were scored outside the treatment fields, particularly in those cases treated with limited brain areas. In a group of six patients with glioblastomas in the posterior

Table V

PATTERNS OF FAILURE IN 105 DEATHS WITH INTRACRANIAL ASTROCYTOMAS

Category	Number of Patients	
	Grades I and II	Grades III and IV
Total No. of Deaths	20	85
Tumor unrelated	1	1
Tumor persistence	1	15
Tumor Recurrence	18	69
(a) Determined*		
Clinically	18	69
Roentgenologically	2	4
Scanning	8	28
Autopsy	3	13
(b) Site with regard to treated fields†		
Inside	8	44
Outside	5	20
Both	5	21
Patterns of Spread:		
Frontal lobe to opposite hemisphere	1	5
Frontal lobe to cribriform plate	0	1
Temporal lobe to midbrain and pons	2	7
Posterior fossa with cervical extension	2	0
Spinal cord seeding	3	4
Multicentric	0	3

* These may be one patient scored into several categories.

† This pertains to boosted fields when given; otherwise considers the irradiated brain area.

fossa (a rare location for these tumors), four clinically seeded subsequently into the spinal cord. One patient had a frontal lobe glioblastoma which eroded the cribriform plate and implanted a year later along the subarachnoid space of the spinal cord. Only three of the 16 posterior fossa Grade I and II astrocytomas had spinal subarachnoid implants. One was detected clinically; the other two were autopsy findings. Two low grade tumors were seen at surgery to project into the subarachnoid space at the level of the first two cervical vertebrae.

EFFECT OF GENERAL FACTORS ON SURVIVAL

Among the factors generally thought to exert an influence on survival were sex, localization, age, and pathology. In our experience, only the last two were relevant to survival.

Age: A statistically significant difference in the survival of patients under 30 years of age *vis-a-vis* older patients was observed. Since this can be an artifact, a further breakdown for each age group was done taking into account the pathological grading. The results appear in Figure 5 and Table III. A statistical difference was present not only in both age groups, but in the tumor grades within each group as well.

Pathology: There was a striking difference among each of the pathological grades. The results appear in Figure 6 and Table III. The estimates for the Grade I group of seven patients are not applicable because, being such a small group of patients, the results are not reliable. There were three deaths in this group and all were supratentorial Grade I tumors. All three patients with cerebellar Grade I tumors are alive and well.

DISCUSSION

Since Grade I astrocytomas are usually treated surgically with good results,[8] very few patients are referred for supplementary

AGE (YRS)	≤30 YRS		>30 YRS	
PATH. (GRADE)	I-II	III-IV	I-II	III-IV
NO. PTS	25	23	19	81
NO. DEATHS	5	15	15	70

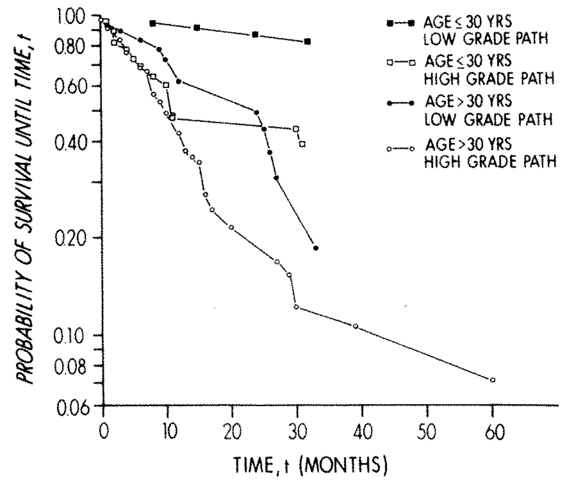

Fig. 5. Failure rate trend of 148 intracranial astrocytomas according to age and pathological grade.

irradiation. We have seen only seven Grade I cases in 15 years; because they constitute a very small sample, no valid conclusions could be drawn. On the other hand, 37 Grade II tumors were seen, but unfortunately were all treated similarly (partial brain irradiation with 5,000 rads) and consequently no dose nor volume effect could be analyzed. Judging by their failure rate (Fig. 6) and the fact that only 54 percent were alive at five years after diagnosis (Table III), perhaps they should be treated as Grade III tumors (higher boosted doses, whole brain irradiation). This idea, although shared by others,[10,28,29] requires further documentation. The majority of the discussion which follows is reserved for the more common glioblastoma multiforme.

CHOICE OF CONVENTIONAL DOSE AND TREATED VOLUME

When glioblastomas are not given the benefit of postoperative irradiation, very few patients survive beyond six months.[16,45] The same could also be said for patients receiving incomplete treatment. Figure 7 represents a scattergram of 104 glioblastomas at one year from pathological diagnosis (a reliable time to assess survival in these tumors). It demonstrates dramatically the shorter life span of patients who were incompletely treated (below 1,000 rets). Of all patients treated under 1,300 rets (roughly 5,000 rads), three of 26 survived; 45 of 78 patients treated over 1,300 rets survived. This difference is overwhelmingly significant. Although much discussion has been conducted in the past regarding the optimal doses that these tumors should receive, it has been generally accepted that doses from 5,000 to 6,000 rads seem appropriate.[2,6,14,19,27–29,36–39,45] This well accepted dose concept has encountered very few, mostly debatable, oppositions.[5,41,46]

PATH. (GRADE)	I	II	III	IV
NO. PTS	7	37	50	54
NO. DEATHS	3	17	39	46

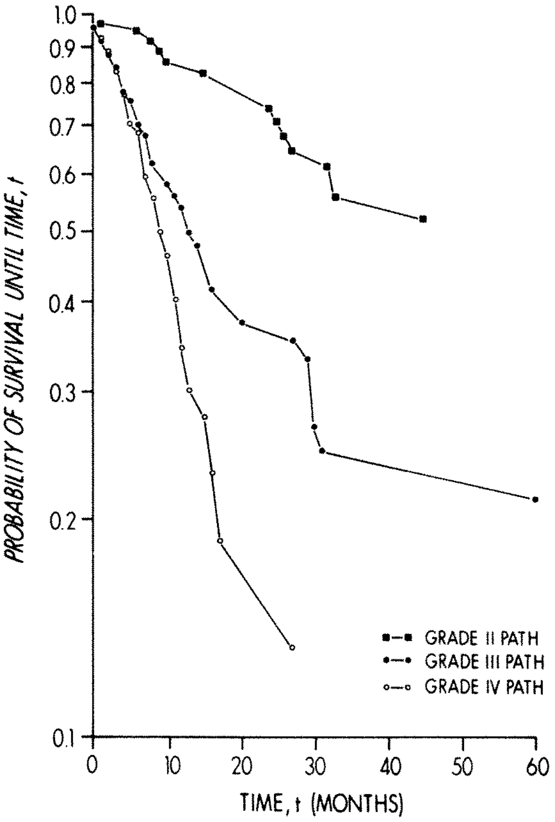

Fig. 6. Failure rate trend of 148 intracranial astrocytomas according to pathological grade.

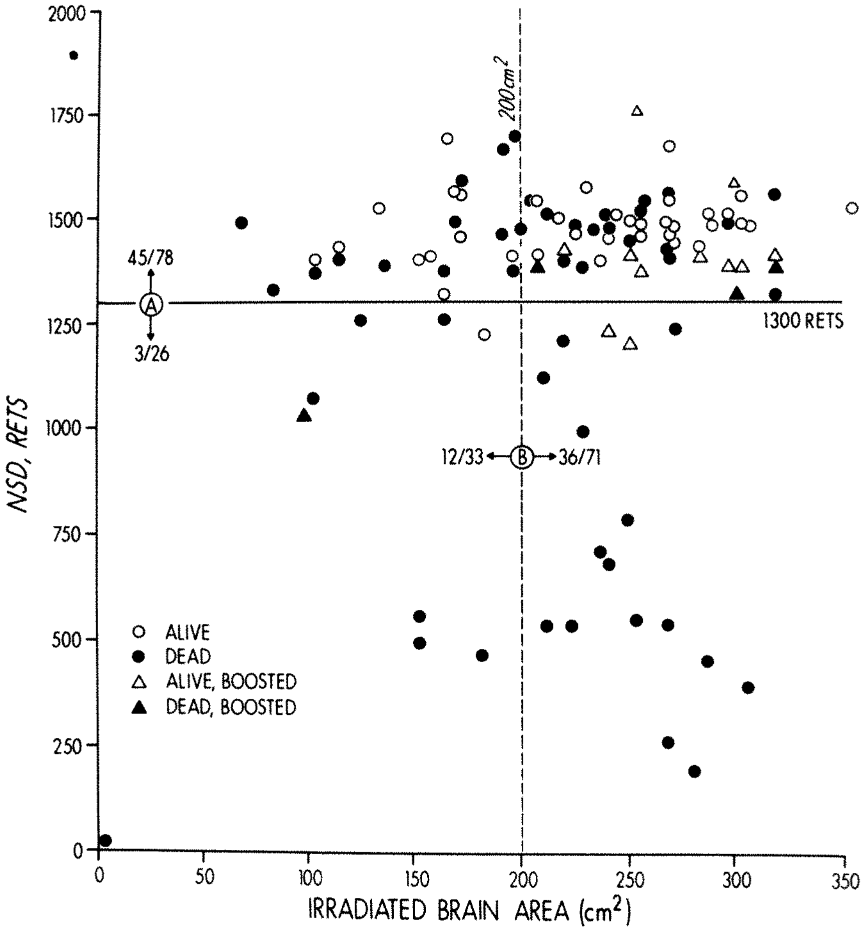

FIG. 7. Glioblastomas: effect of dose and irradiated area on one year survival. Scattergram of 104 glioblastomas one year after diagnosis. Only brain doses are considered; booster doses delivered to small areas are excluded. 200 cm^2 = minimal (average) area to represent whole brain irradiation; 1,000 rets = dose under which patients were considered incompletely treated; 1,300 rets = minimal (optimal) dose that must be delivered, approximately 4,500 rads. (*A*) Establishes a comparison of alive/dead cases treated with doses above or below 1,300 rets. (*B*) Establishes a comparison of alive/dead cases treated with areas over or under 200 cm^2.

Recently accumulated evidence has shown an increased survival of patients with glioblastomas treated with total instead of partial brain irradiation.[2,27,46] As a rule, it is now a widely accepted concept which has been challenged on rare occasions without reproducible data.[38] In the same scattergram presented in Figure 7, 36 of 71 patients treated to brain areas over 200 cm^2 (minimal average area to represent whole brain) compared with twelve of 33 patients treated with partial brain fields survived. Finally, on the same scattergram, if one combines both treatment factors (dose and irradiated area) the best survival is observed for patients treated with whole brain doses above 1,300 rets (Fig. 4, Table IV).

REASONS FOR LOCAL FAILURE

Local tumor recurrences overwhelmingly constitute the major therapeutic failure pathway. Several reasons could be offered to explain failure to control and cure glioblastomas and all are interrelated to yield an almost fatal outcome. Many attempts to overcome some of them have been made without impressive results.

Necrosis and Hypoxia: Glioblastomas are characterized by either focal or diffuse areas of necrosis, particularly toward the center, surrounded by hypoxic tumor cells which are protected by virtue of their low oxygenation against the effects of X or gamma radiation.[27] These central cores of radioresistant cells prevent suitable sterilization with conventional dose schedules. Hyperbaric oxygen therapy,[27] split radiation regimens,[2] superfractionation,[42] and radiosensitizers[31] have been tried in vain in the past to overcome these difficulties. In addition to cell necrosis (in the tumor originally, induced by treatment, or both), there is considerable cell attrition occurring normally; this leads to a release of lysosomal enzymes resulting in secondary cerebral edema and brain swelling.[25] If steroids are not used to overcome this difficulty, one may expect more anoxia, decreased diffusion capacity of already impaired vascular channels, and less effective treatment. Clinical symptoms developing as a direct result of this situation may interrupt or restrain treatment leading to a loss in time-dose relations. Since the skull limits the volume increase of intracranial contents, cerebral edema from necrotic debris or tumor hemorrhage from therapy could conceivably terminate survival.[3] Finally, the architecture of these tumors is such that the blood flow varies tremendously because of vascular shunts that exist toward the center. This creates islands of hypoxic cells; it also allows systemic chemotherapeutic agents to by-pass some tumor cells.[3,4,13,48–50] Perhaps intrathecal drugs could overcome this obstacle.

Cell Kinetics and Bioenergetic Pathways: Malignant glial cell kinetics studies have given information that a significant number of cells may replicate "amitotically" and that an exceptionally high proportion of malignant cells, both *in vivo* and *in vitro* remain in the G_1 phase.[23,25] This may account for the relative ineffectiveness of conventional therapeutic modalities. Studies are in progress to use sodium warfarin in an attempt to concentrate cells in the S-phase and thus enhance the effectiveness of radiation and chemotherapy.[25] On the other hand, tumor cells in hypoxic areas may survive by catabolizing their own nucleic acids and regrow when a new vascular supply is re-established.[24] This would allow some cells to escape any conventional treatment offered.

Rapid Intracranial Tumor Spread and Multicentricity: Glioblastomas are seldom cystic, but rather diffuse, infiltrating neoplasms which are commonly found in autopsies to have been more extensive than suspected clinically.[10,29] In addition, they can occasionally be multicentric.[39] All this leads into the issue of "geographical misses" which we believe constitute an essential part of the failure pathways. As the tumor reaches the brain surface, it readily infiltrates the leptomeninges, and microscopic invasion of cerebral subarachnoid spaces is frequently found.[39,45] This in turn leads to freely circulating clonogenic cells capable of re-implanting in the primary site or quite distant from it. The cerebral subarachnoid space then becomes the target for whole brain irradiation and it could be underdosed (by virtue of falling into the penumbra) if adequate margins are not offered. In addition, glioblastomas show certain spread patterns for each location of the brain where they occur. They are extremely common in the frontal lobe where the tumor has been seen to cross the corpus callosum into the opposite hemisphere in a butterfly pattern of spread. Glioblastomas of the temporal lobe (which rank second in order of frequency), as well as deeply situated midline tumors, can invade into the middle cranial fossa and extend to the midbrain and pons.[10,17,29] Consequently, the use of small localized fields to boost ill-defined target volumes can account for geographical errors.

Extracranial Spread: Less frequently, spread beyond the cerebrum occurs. A frontal lobe glioblastoma has been observed by us to erode the cribriform plate and seed months later into the spinal subarachnoid space. Glioblastomas of the posterior fossa are rare, but in four of six such instances in our cases, spinal implantations have subsequently occurred. Seeding into the subarachnoid space of the spinal cord by glioblastomas is no longer considered an extremely rare phenomenon.[7,15,39,44,45] A very recent report[7] has produced evidence that 60 percent of almost 100 cases of primary brain tumors with cerebrospinal fluid seedings were glioblastomas. In 50 percent of these instances, seeding was only microscopic, but the other half had macroscopic nodules. Whether or not seedings become symptomatic is uncertain. All our patients with seeding had symptoms and roentgenological confirmation of metastases. Unless millipore filter examination of the cerebrospinal fluid is done to exclude this possibility, it is likely that clonogenic cells may re-seed inside the cranium after treatment. Finally, on rare instances, glioblastomas can promote extracranial metastases, usually after surgical decompression,[18] or invade the dura where cells are lodged outside the craniospinal axis, usually after survival has been sufficiently prolonged by radiation therapy.[39]

Impaired Immunologic Mechanisms: In glioblastomas, as in any other form of cancer, there are impaired immunologic mechanisms in the host which aid in precipitating the ultimate failure.[9,33,35] It is possible, consequently, that these patients could conceivably mobilize a cell-mediated immune response which coexists with tumor progression. Recent attempts to use specific active immunotherapy in patients after adequate treatment are exploring this possibility.[4,35]

CHOICE FOR HIGHER DOSES AND WHOLE BRAIN IRRADIATION

Although it is true that glioblastomas, because of their diffuse and extensive spread pattern, require whole brain irradiation, they also, because of their anoxic component, may require higher doses than those commonly employed if an increased survival is desired. Nevertheless, radiation therapy probably exerts little or no effect on certain immune and radiobiological factors of the tumor and the host which may be directly responsible for failure. Since through an increase in dose and extension of fields only partial failure pathways are encompassed in these tumors, the quality of survival becomes an important consideration in the effectiveness of treatment. The value of higher doses in the treatment of these tumors is discussed in a separate report.[40]

SPECIAL CONSIDERATIONS

Pathology: We believe that the use of the grading system of Kernohan and Sayre[22] simplifies the classification of intracranial astrocytomas and correlates best with prognosis. It is perhaps better not to cluster these tumors into Grades I–II and Grades III–IV. Grade II lesions are perhaps closer to III than to I in prognosis; in glioblastomas, the majority of the long-term survivors are Grade III while Grade IV seldom shows survivors at five years. This is clearly shown in our data (Table III, Fig. 6) as well as by other authors.[22,41,43,47]

Surgery: A better survival has been reported in irradiated patients whose tumors were excised completely.[12,14,19,45] We have confirmed this with our present series for each pathological grade group (Table III, Fig. 3). This statement must be weighed against a relatively high operative mortality. Surgical mortality has been reported to be 0–20 percent for low-grade astrocytomas and 16–38 percent for glioblastomas.[14,16,20] We believe that the extent of surgery is a function of the tumor location and size and consequently is directly related to cell kill and survival.

Age: Although it is true that glioblastomas are rare tumors in children,[1,26,34,36,51,52] we had ten percent of patients below age 15 and 20 percent under age 30 (Fig. 1). Patients 30 years of age or under survive longer than older individuals for each pathologic grade group (Table III, Fig. 5). This finding has not been confirmed in any of the literature reviewed.

RECOMMENDATIONS

Glioblastoma multiforme should be treated with whole brain irradiation (5,000–6,000 rads). The field should be generous enough to encompass the entire middle cranial fossa and the cerebral subarachnoid space. In addition, the primary target volume should be boosted to at least 7,000 rads. Boosting fields require ample margins and either three portals or a parallel arrangement when the tumors are deep or centrally located to avoid missing possible crossovers to the opposite hemisphere. More peripheral tumors can be boosted with wedges. The daily fractionation for five weekly fractions varies from 150 to 200 rads where 180 rads per fraction becomes a suitable compromise.

Glioblastomas seldom occur in the posterior fossa. When they are found in this location, we are convinced, by virtue of our failures, that craniospinal irradiation is indicated. The field arrangement then resembles that of a medulloblastoma except that the doses delivered are higher. Millipore filter cerebrospinal fluid examination is done; when positive for malignant cells, 4,000 to 4,500 rads are given to the spinal cord; when the results are negative, treatment is elective (3,500–4,000 rads).

Grade II astrocytomas, based on our failure patterns, their relatively poor survival at five years, and the opinion of other respected investigators,[10,28,29] should perhaps be treated with whole brain irradiation (4,500 rads) plus an additional 1,000 rads to the primary target volume. Again, millipore filter cerebrospinal fluid examination is done for posterior fossa tumors; if positive, craniospinal irradiation is indicated. When posterior fossa Grade II tumors are seen at surgery to be extensive or to project into the upper cervical subarachnoid space, or both, a modification of the whole brain field to encompass the first few cervical vertebrae is advised.

The use of higher doses in intracranial astrocytomas may not increase five year survival figures significantly. It has indeed increased one year survival of glioblastomas to almost 80 percent. The improved quality of survival of patients, irrespective of dose or grade, treated with postoperative irradiation constitutes the most solid, justifiable, and unquestionable reason for its use in the management of these tumors.

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PHARMACO-KINETICS OF CURRENT SKELETAL-SEEKING RADIOPHARMACEUTICALS*

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ABSTRACT:

The blood clearance of all current bone-seeking radiopharmaceuticals is biexponential during the first four hours after injection. Exponent I represents bone uptake and its clearance half-time is less than 30 min. Exponent II represents mainly urinary excretion and its clearance half-time varies from 168 to 512 min. The blood background is highest with ^{99m}Tc-labeled polyphosphate (Tc-Poly) and lowest with sodium fluoride (F-18); ^{99m}Tc-labeled diphosphonate (Tc-Dip) and ^{99m}Tc-labeled pyrophosphate (Tc-Pyro) show intermediate blood levels. The slower blood clearance of ^{99m}Tc-phosphate complexes in comparison with F-18 is due primarily to their increased protein binding. Tc-Poly blood clearance, which is slower than that of Tc-Dip and Tc-Pyro, is due primarily to its increased red cell binding and the larger size of its molecule. Bone uptake and urinary excretion of all ^{99m}Tc-labeled phosphate complexes are approximately the same: in the range of six to ten percent in the blood, 30–33 percent in the urine, and 55–58 percent in the bone and other tissues. F-18 concentration in the bone is almost 1.5 times that of the ^{99m}Tc-labeled phosphate complexes. The sensitivity and resolution of lesions are identical for all ^{99m}Tc-labeled phosphate complexes and are far better than those for F-18. No toxicity is noted with the amount of phosphate present in the marketed kits, and it appears reasonable to use the minimal amount so long as efficiency is not compromised.

THE introduction of ^{99m}Tc-labeled phosphate complexes in 1971 was a major breakthrough in skeletal imaging in nuclear medicine.[18] Technetium 99m-labeled polyphosphate, introduced by Subramanian and McAfee,[19] was immediately followed by ^{99m}Tc-labeled diphosphonate[3,20,22] and pyrophosphate.[14] All of these complexes have subsequently established themselves as useful agents for skeletal imaging. For the first time, the clinician is faced with the problem of choosing the optimal agent. It has consequently become important to study these agents in man in order to understand more about their comparative biological behavior.

At the Wadsworth Hospital Center we have undertaken a clinical study in which two agents are assessed in succession, in a paired study. Technetium 99m-labeled polyphosphate serves as the common agent for all. Earlier, in 1969, it was concluded after a study of all the then available bone-seeking radionuclides that sodium fluoride F-18 was the best agent.[21] In our first study, therefore, we compared it with ^{99m}Tc-polyphosphate (Tc-Poly), concluding that Tc-Poly was better.[9,10] In our second study we

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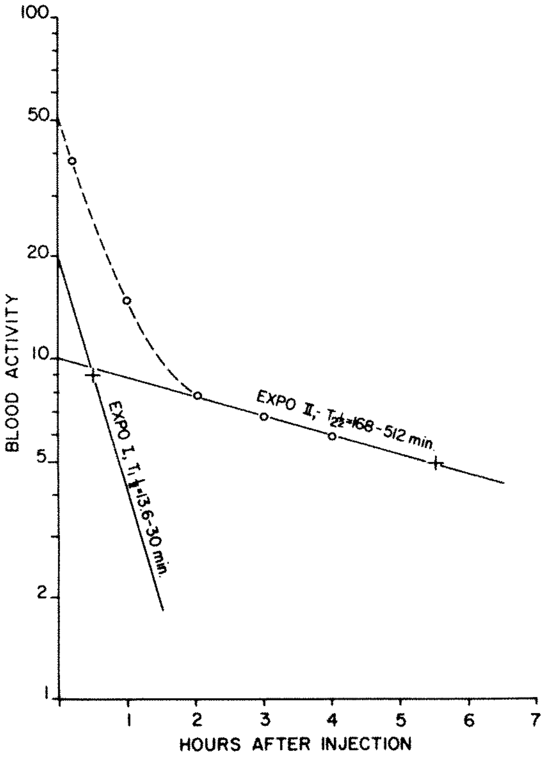


Fig. 1. Typical blood clearance of skeletal-seeking radiopharmaceuticals, showing a biexponential curve. (Note addendum.)

compared Tc-Poly with ^{99m}Tc-labeled diphosphonate,[11] and in the third and last study we compared Tc-Poly with ^{99m}Tc-labeled pyrophosphate.[12] After comparison and evaluation of two agents in succession, the need became obvious to compare all the agents with each other to permit some preliminary conclusions as to their biologic similarities and differences. In this paper we present a summary of the comparative kinetics data and comment on the images obtained in man using these agents. The data presented and the conclusions drawn refer only to the compounds that we have used.

MATERIAL AND METHOD

The methods and the procedure used in this study have been described elsewhere in great detail.[9–12] The study involved a total of 31 patients with suspected bone lesions studied with Tc-Poly and repeated, in ten patients, with F-18;[9,10] in eleven patients, with ^{99m}Tc-labeled diphosphonate (ethane-1-hydroxy-ethylidene-1, 1-disodium phosphonate) (Tc-Dip); and, in the remaining ten patients, with ^{99m}Tc-labeled pyrophosphate (Tc-Pyro). All the patients were studied without special preparation prior to the injection of the radiopharmaceutical and were allowed *ad libitum* fluid intake after the injection. In the case of the technetium 99m-labeled agents, 15 mCi each of Tc-Poly, Tc-Dip, and Tc-Pyro were used; in the case of F-18, 2–4 mCi were injected intravenously after voiding. Blood samples were drawn at ten and 30 min and at one, two, three, and four hours after injection, in test tubes containing an anticoagulant. Urine was collected in hourly samples for four hours, except in the case of patients studied with F-18. An aliquot of blood, plasma, and urine was counted with an aliquot of the diluted standard and the results were expressed as percent dose per liter of blood or plasma, or as percent dose excreted in urine at each hour and at the end of four hours. The radioactivity, both

Table I

THE KINETICS OF SKELETAL-SEEKING RADIOPHARMACEUTICALS

Radiopharmaceutical	Blood Clearance (T-1/2 min.)		Plasma (1 hr.)	
	Exponent I	Exponent II	Percent Protein Bound	Percent Free
Fluorine 18	24	198	14.2	85.8
^{99m}Tc-polyphosphate	13.6–30.0	264–512	75.4	24.6
^{99m}Tc-diphosphonate	18	168	84.2	15.8
^{99m}Tc-pyrophosphate	14	380	84.3	15.7

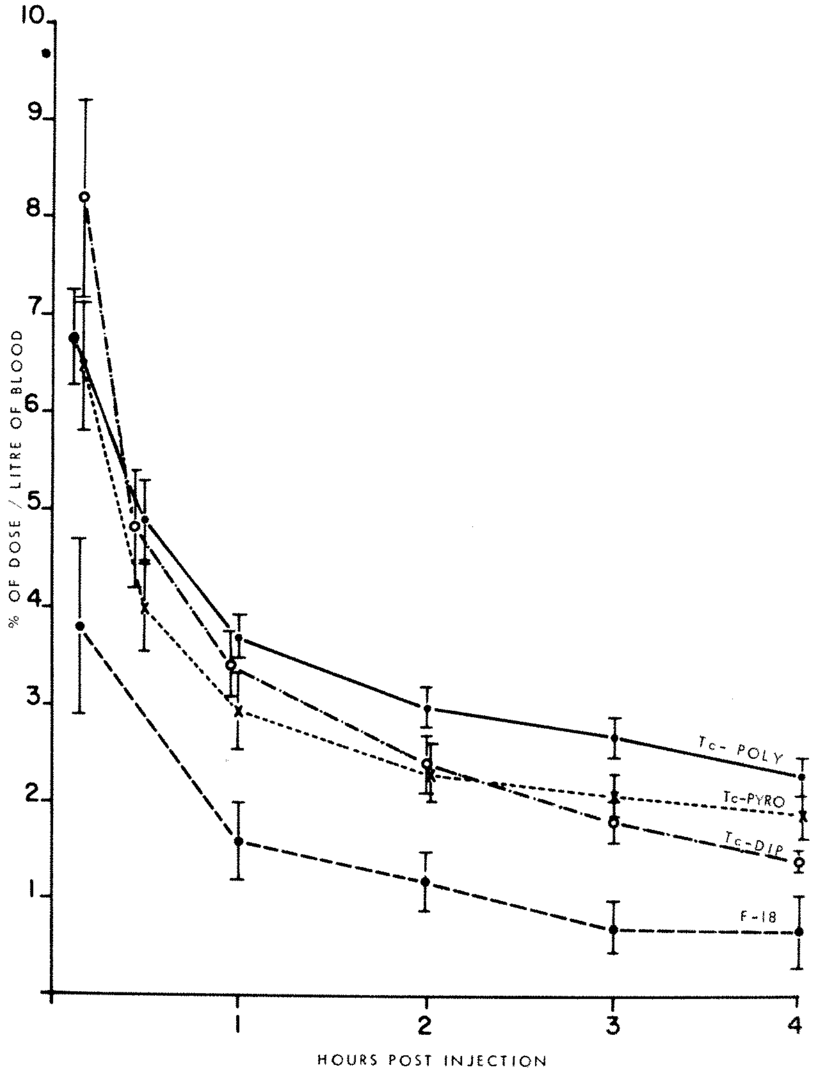


Fig. 2. Comparative four hour clearance of skeletal-seeking radiopharmaceuticals. The blood levels at four hours are significantly different ($p<0.05$).

free (not bound) and bound to plasma protein, was determined as described.[9–11] The radioactivity bound to each protein fraction was determined by Microzone protein electrophoresis. Basal and one hour postinjection serum levels of ionized and total calcium, inorganic phosphorus, alkaline phosphatase, and total protein were measured.

Skeletal images were obtained at varying times to determine the most ideal imaging interval after injection. The images were obtained with a Picker five inch crystal rectilinear scanner[10] or an Anger scintillation camera fitted with a high-resolution or high-sensitivity[10,11] or a Divcon collimator,[12] usually starting after two and one-half hours postinjection. Images of identical regions were obtained at identical time intervals and the time required to accumulate a 500,000 count with both agents was noted. Images were assessed for the number of lesions (sensitivity) as well as for the clarity of the abnormal region contrasted against normal bone (resolution). Skeletal surveys were obtained by roentgenography.

TABLE II

COMPARATIVE CLEARANCE OF SKELETAL-SEEKING RADIOPHARMACEUTICALS FROM BLOOD

Radiopharmaceutical	Time After Injection									
	10 min.	30 min.	1 hr.		2 hr.		3 hr.		4 hr.	
	B	B	B	U	B	U	B	U	B	U
Fluorine 18										
Mean (N=10)	3.80	—	1.6	—	1.2	—	0.7	—	0.7	—
S.E.	0.90	—	0.4	—	0.3	—	0.2	—	0.4	—
^{99m}Tc-polyphosphate										
Mean (N=31)	6.80	4.4	3.6	13.7	2.9	21.9	2.6	26.8	2.3	30.7
S.E.	0.42	0.4	0.21	1.6	0.17	3.0	0.16	2.5	0.14	0.7
^{99m}Tc-diphosphonate (EHDP)										
Mean (N=11)	8.2	4.8	3.5	13.4	2.5	20.9	1.8	30.9	1.4	33.8
S.E.	1.2	0.6	0.4	2.1	0.3	2.6	0.2	3.0	0.2	4.6
^{99m}Tc-pyrophosphate										
Mean (N=10)	6.4	4.0	3.0	16.4	2.3	22.8	2.1	28.3	1.9	31.7
S.E.	0.7	0.4	0.4	2.6	0.3	3.3	0.3	3.5	0.2	3.7

B = percent dose per liter of blood.
U = percent dose excreted in urine.
N = number of patients.
S.E. = standard error.

RESULTS

During the initial four hours after injection, the blood clearance of all the bone-seeking radiopharmaceuticals is biexponential (Exponent I and Exponent II), as shown in Figure 1. Exponent I, which we hypothesize to represent bone uptake, has a clearance half-time (T_1–1/2) of 13.6 to 30 min. Similarly, Exponent II represents mainly renal clearance and has a blood clearance half-time (T_2–1/2) of 168 to 512 min for the four agents (Table I).

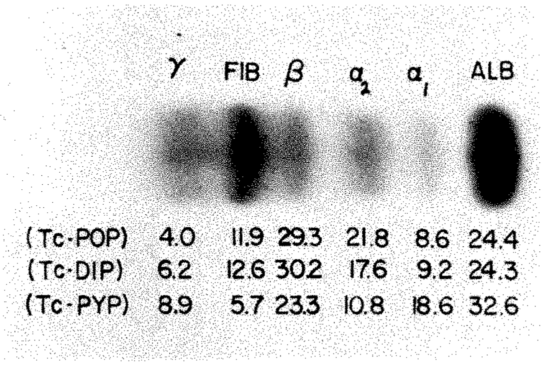

γ FIB β α₂ α₁ ALB
(Tc-POP) 4.0 11.9 29.3 21.8 8.6 24.4
(Tc-DIP) 6.2 12.6 30.2 17.6 9.2 24.3
(Tc-PYP) 8.9 5.7 23.3 10.8 18.6 32.6

FIG. 3. Protein labeling of ^{99m}Tc-phosphate complexes. The figure shows the percentage of total protein activity associated with each fraction at one hour.

Blood levels at different time intervals are shown in Figure 2. The blood clearance is faster with F-18 and slower with Tc-Poly; Tc-Dip and Tc-Pyro fall in between. Thus the background radioactivity is highest with Tc-Poly and lowest with F-18. The differences in blood radioactivity among these agents at four hours are statistically significant ($p < 0.05$). Table II shows the mean percentage of the administered dose per liter of blood associated with each agent at different time intervals. With ^{99m}Tc phosphate complexes, the blood radioactivity is primarily associated with plasma protein (Table I), the globulin fractions binding most of the radioactivity. Albumin, even though it represents more than 50 percent by weight of total plasma protein, binds less than 33 percent of the total protein radioactivity (Fig. 3).

Cumulative urinary excretion is almost identical for all ^{99m}Tc-labeled agents, with a four hour mean excretion value of 33 percent. Tc-Pyro is excreted at a relatively faster rate during the first hour, but the

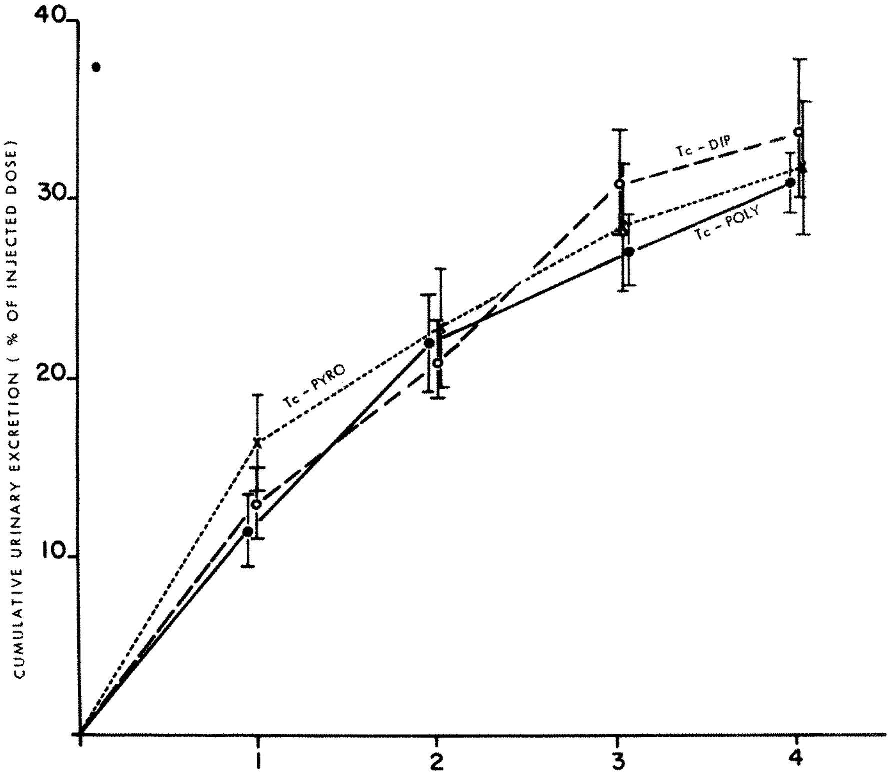


Fig. 4. Urinary excretion of ^{99m}Tc-phosphate complexes in man.

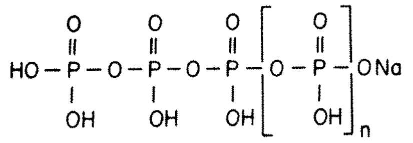
total excretion at the end of four hours is similar to that of the others (Fig. 4).

Tc-Poly and Tc-Pyro had no significant effect on the one hour serum levels of ionized or total calcium, total protein, inorganic phosphorus, and alkaline phosphatase.[12] *In vivo* stability and *in vitro* labeling were consistently good with Tc-Poly and Tc-Pyro[9,10,12] and were occasionally variable with Tc-Dip.[11]

DISCUSSION

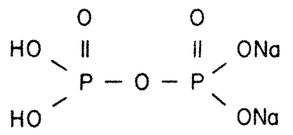
The comparative chemical structures and salient biological features of the ^{99m}Tc-labeled agents are shown in Figure 5. Polyphosphate and pyrophosphate both have P-O-P linkages and differ from each other in constitution and in chain length, polyphosphate having a variable chain length with four to 50 atoms of phosphorus per molecule and pyrophosphate having a discrete chain length with two phosphorus atoms per molecule. Both are biodegradable by phosphatase enzymes produced in the body. Diphosphonate differs from these two agents in chemical structure, having a P-C-P instead of a P-O-P linkage. There is as yet no known serum enzyme that hydrolyzes diphosphonate. Pyrophosphate and diphosphonate are smaller molecules with molecular weights of 250 and 246, respectively; while the molecular weight of polyphosphate may vary from 600 to 6,000 depending upon the chain length. It has been suggested recently in one study that ^{99m}Tc-labeled pyrophosphate may in fact have a cyclic structure;[13] however, this finding has not yet been confirmed.

All bone-seeking agents are cleared from the blood after intravenous injection in a biexponential fashion (Fig. 1). We hypothesize that Exponent I represents mainly bone uptake, and Exponent II renal clearance (Fig. 1). The clearance half-time of Exponent I of less than 30 min suggests that the bone uptake is a rapid biologic

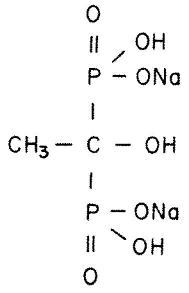


$$HO-\underset{OH}{\overset{O}{\overset{\|}{P}}}-O-\underset{OH}{\overset{O}{\overset{\|}{P}}}-O-\underset{OH}{\overset{O}{\overset{\|}{P}}}-\left[O-\underset{OH}{\overset{O}{\overset{\|}{P}}}\right]_n-ONa$$

POLYPHOSPHATE (MONOSODIUM POLYPHOSPHATE) HYDROLYZABLE, NON-DISCRETE CHAIN LENGTH



PYROPHOSPHATE (DISODIUM PYROPHOSPHATE) HYDROLYZABLE, DISCRETE CHAIN LENGTH



DIPHOSPHONATE (DISODIUM ETHANE-1-HYDROXY-1, 1-DIPHOSPHONATE) HYDROLYZABLE, DISCRETE CHAIN LENGTH

FIG. 5. Comparative chemical structures of ^{99m}Tc-phosphate complexes.

process. The low clearance of Tc-Poly from blood in comparison with Tc-Dip and Tc-Pyro (Fig. 2) can be attributed to its relatively firm red blood cell binding and larger molecular size.[9] The fast clearance of F-18 in comparison with ^{99m}Tc-labeled agents is facilitated by its relatively lesser protein binding (Table 1).

Figure 6 shows the compartmental distribution of bone-seeking radiopharmaceuticals four hours after injection. The blood volume was assumed to be five liters. The four hour urinary excretion of F-18, which was obtained from a published report, represents the mean value of five patients.[21] The amount taken up by bone and other tissues was derived by subtracting the sum of blood and urine radioactivity from the total injected dose.

At four hours, 3.5 percent of F-18, 9.2 percent of Tc-Poly, 7.0 percent of Tc-Dip, and 9.5 percent of the total dose of Tc-Pyro was circulating in the blood. It is to be noted that, in a paired study in ten patients, the blood levels of Tc-Pyro were significantly lower than those of Tc-Poly.[12] This difference is not seen in Figure 6, which (as pointed out earlier) includes 20 other patients who were not studied with Tc-Pyro.

Among the soft tissues the kidneys were the only organs visualized consistently with ^{99m}Tc-labeled phosphate complexes. The kidney images were in every case superior with Tc-Poly and Tc-Pyro, but were less often superior with Tc-Dip. The reason for this disparity appears to be the relatively larger retention by the kidneys of Tc-Poly and Tc-Pyro.[11,12] In animals, three to four percent of the dose of Tc-Poly[18,19] and Tc-Pyro,[8] but less than two percent of the dose of Tc-Dip,[3] was retained by the kidneys. Kidney images were consistently inferior with F-18 and did not correlate with other kidney function tests.[10,15] The kidney images obtained with ^{99m}Tc-phosphate complexes were of such good quality that many clinically unsuspected renal lesions first detected during bone imaging were later confirmed by other tests. The patient in Figure 7 had an obstruction of the right ureter which was seen first during bone imaging with Tc-Poly and later confirmed with an intravenous pyelogram. We have made it a policy to comment on kidney image status whenever an abnormality was detected during bone study. So far, we have found no false-positive images.

Skeletal images obtained with ^{99m}Tc-phosphate complexes are of excellent quality, without differences in sensitivity or resolution. In contrast, skeletal images obtained with F-18 are relatively much inferior in both sensitivity and resolution.[7,16] The images obtained with ^{99m}Tc-phosphate complexes are more sensitive than the serum levels of alkaline phosphatase, calcium, or inorganic phosphate in the detection of skeletal lesions.[7,13]

Bone images with ^{99m}Tc-complexes, even

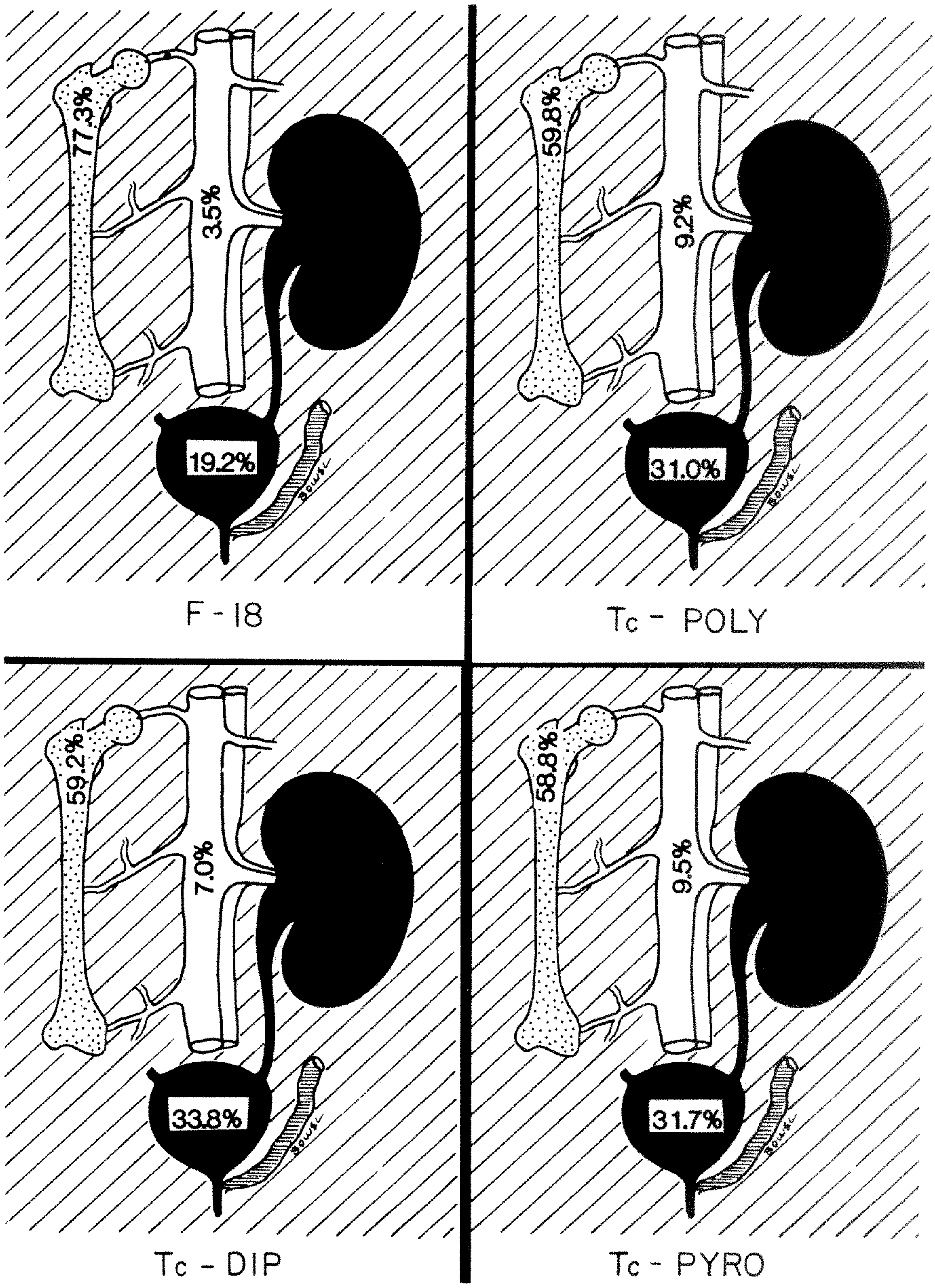


FIG. 6. Body distribution of skeletal-seeking radiopharmaceuticals at four hours.

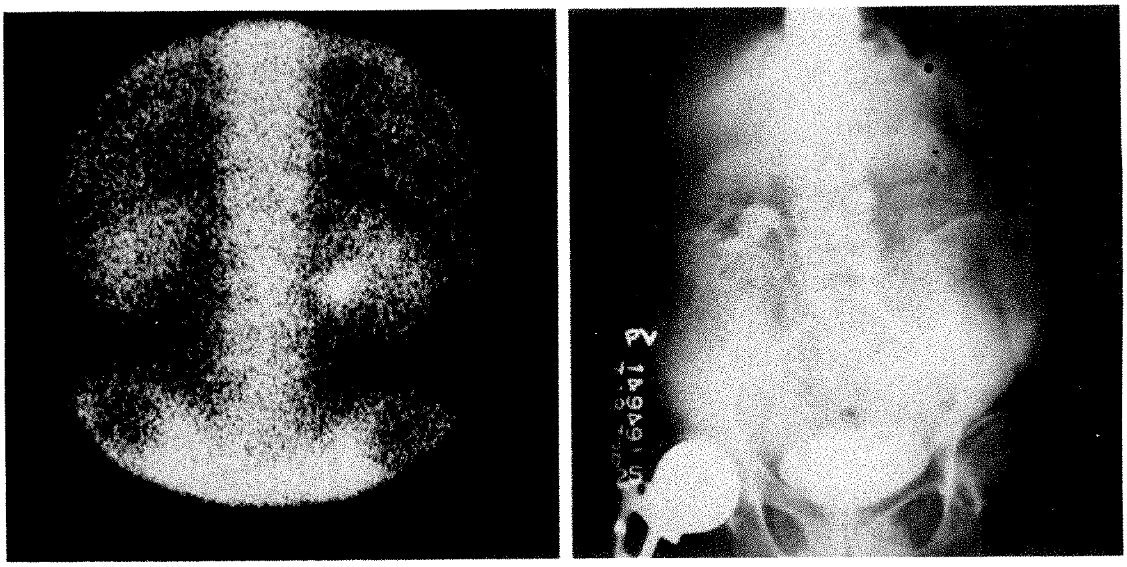


FIG. 7. Right ureteral obstruction, detected first with Tc-Poly (posterior view) and later confirmed with intravenous pyelogram (anterior view).

though very revealing, are nonspecific. The ^{99m}Tc-phosphate complexes are also concentrated in many non-skeletal lesions like cerebral[6] and myocardial infarctions,[1] breast neoplasms,[5] and arthritis.[4]

Generally, images obtained with Tc-Poly require relatively longer times to accumulate an identical number of counts from the same region of the body than images obtained with Tc-Dip and Tc-Pyro. Clinically satisfactory images were obtained with all three agents, but the images obtained with Tc-Pyro were consistently superior.[11,12]

No toxicity was noted with any one of these agents. The amount of phosphate complexes present in each vial was 40 mg with polyphosphate, 1 mg with diphosphonate, and 15.4 mg with pyrophosphate. These are the maximum amounts of phosphate complexes that can be injected into any single patient using one whole vial. In animals, it has been shown that 20 mg or more of Tc-Pyro per kilogram of body weight produced hypocalcemia and tetany prior to the onset of (LD$_{50}$) death effect. In rats, the LD$_{50}$ at 5 min was 41.0 mg/kg body weight with Tc-Pyro and 29.4 mg/kg with Tc-Poly, suggesting that at the LD$_{50}$ level (5 min), Tc-Poly is 1.4 times more toxic than Tc-Pyro.[17] For a man of 70 kg body weight, the contents of a single vial of polyphosphate (40 mg) would amount to 0.6 mg/kg and those of a vial of pyrophosphate (15.4 mg) would amount to 0.2 mg/kg. These levels are well below the dose (20 mg/kg) required to produce hypocalcemia in rats. However, it would appear beneficial to reduce the phosphate dose, if it could be done without compromising efficiency.

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Sodium fluoride, F-18, was obtained through commercial sources. Polyphosphate kits were supplied through the courtesy of New England Nuclear Corporation, North Bellerica, Mass., and Diagnostic Isotope, Upper Saddle River, N.J. Diphosphonate (EHDP) kits were supplied through the generosity of Medi-Physics, Inc., Emeryville, Calif. Pyrophosphate kits were supplied, and a grant in partial support of the project was made, through the

courtesy of Mallinckrodt Radiopharmaceuticals, St. Louis, Mo.

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ADDENDUM:

The kinetic data obtained after the completion of the work presented here indicate that the blood clearance of the skeletal-seeking agents may actually be triexponential; the fastest component having a $T_{\frac{1}{2}}$ clearance time of less than 5 minutes. This component was not noticed in the data presented in this paper as the first blood sample was obtained 10 minutes after injection. The third component (fastest) seems to represent mainly the equilibration in the extravascular space.

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CANCER OF THE UNDESCENDED OR MALDESCENDED TESTIS*

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ABSTRACT:

An analysis of 45 cryptorchids (by history or examination) with a testicular cancer treated at Memorial Hospital, between 1934 and 1973, is presented. Twenty-five patients had the cryptorchid state repaired at ages four to 27 years, either spontaneously or by orchiopexy or hormonal therapy. Ipsilateral (24) or contralateral (one) intrascrotal testis tumors developed four to 47 years later. Twenty cryptorchid patients presented with ipsilateral inguinal (eleven), abdominal (seven), or contralateral intrascrotal (two) tumors. There were 18 pure seminomas, 17 embryonal carcinomas, nine teratocarcinomas, and one reticulum cell sarcoma. Five year survival rates as estimated by the product-limit method were 60 percent for the unrepaired cases and 41 percent for the repaired cases. The survival seems to follow histologic type and anatomical stage, whether the testis is within the scrotum or not. Five year survival similarly estimated was 78 percent in the seminomas and 29 percent in the other tumors. Twelve of thirteen survivors (including nine with seminoma) received postoperative irradiation to the regional lymphatics and eleven were without recurrent tumor for periods ranging from six to 28 years.

THE role of cryptorchidism in the genesis of testicular tumors has been a subject of considerable interest. About 86 percent of fetal testes descend by the eighth fetal month, and some of the remainder will reach the scrotum before the fifth day of postuterine life.[8,26] Cryptorchidism occurs in only about one out of 500 men, but the probability of a malignancy developing in an undescended testis is 20 to 48 times greater than in a normally descended testis.[1-34]

The purpose of this study is to describe the evolution and biological behavior of testicular cancer in historically or clinically cryptorchid patients in an attempt to currently categorize prognostic factors and to better plan therapeutic approaches.

MATERIAL AND METHOD

During the 40 year interval extending from 1934 to 1973, 45 patients with a testicular cancer and a historical (prior) or clinical (current) evidence of cryptorchidism were found among 1,561 cases of malignant testicular tumors registered at the Memorial Sloan-Kettering Cancer Center.

Twenty-five patients presented with intrascrotal testis tumors and had a past history of cryptorchidism repaired four to 47 years earlier. Repair was by orchiopexy at age four to 27 years in 15 patients, following hormonal therapy at age six to eleven years in six, and spontaneously between ages eight to 13 years in four patients.

Current evidence of cryptorchidism was noted in the other 20 patients including 18 with inguinal or lower abdominal tumors, and two patients who had tumors of a normally descended testis with contralateral cryptorchidism (Table 1).

There were 18 seminomas, 17 embryonal carcinomas, nine teratocarcinomas, and one reticulum cell sarcoma. The tumors were staged according to the initial gross and

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Table I

TYPE AND SIDE OF MALIGNANT TESTIS IN HISTORICAL OR CURRENT CRYPTORCHIDS

Type of Malignant Testis	No.	Side	
		Right	Left
A. Unrepaired Cryptorchid Testis	18		
I. Abdominal		3	4*
II. Inguinal		5†	6
B. Repaired Cryptorchid Testis	24		
I. Orchiopexy		2	12‡
II. Hormonal therapy		5	1
III. Spontaneous descent		4	
C. Normally Descended Testis	3		
I. Unrepaired contralateral cryptorchidism			2
II. Repaired§ contralateral cryptorchidism			1
Total	45	19	26

Two* and one† of these patient presented with bilateral cryptorchidism.
‡ Two had bilateral orchiopexy.
§ By orchiopexy.

microscopic extent of spread into three stages: Stage I: no demonstrable regional lymphatic or distant metastases; Stage II: para-aortic or pelvic (regional) lymph node involvement; Stage III: distant spread. This clinicopathologic staging, modified from Boden and Gibb,[3] was variously achieved by preoperative chest roentgenograms, bipedal lymphangiograms, exploratory laparotomy, and postoperative histological examination of the operative specimens.

The median interval from treatment of testicular cancer until last follow-up or death was two years in the 25 repaired cases and four years in the 20 unrepaired cases. Eleven patients, including nine repaired and two unrepaired cases, are alive after treatment less than five years ago. Confirmatory autopsy data were obtained in five repaired and five unrepaired cases.

CLINICAL FEATURES

All patients were male caucasians with an age range of 15 to 60 years and a median age of 34 years. The majority (34/45) were between ages 21 to 40 years (Fig. 1). The median age in the 25 repaired cases at the time of repair of the cryptorchid state was eleven years and at the time of tumor detection was 34 years, with a median interval of 20 years in between. The 20 unrepaired cryptorchid cases also had a median age of 34 years when their tumors were detected (Table II).

Sixty percent of the patients complained of a testicular swelling or pain, and 40 percent experienced pain or a lump in the groin or lower abdomen (Table III). The duration of symptoms prior to diagnosis varied from one week to three years, with a median duration of two months.

Half of the patients had an enlarged intrascrotal testis and one-third had a palpable mass in the groin or lower abdomen. Unilateral or bilateral cryptorchidism was noted in 44 percent, and an orchiopexy scar in 33 percent of patients. An atrophic intrascrotal testis was found in 29 percent, and an indirect inguinal hernia or a herniorrhaphy scar in nine percent of cases. Enlarged supraclavicular or inguinal lymph nodes were observed in eleven percent and bilateral gynecomastia in nine percent of patients.

Preoperative investigations revealed pulmonary or mediastinal lesions on chest roentgenograms in 24 percent, para-aortic or pelvic lymphadenopathy on lymphangiography in 18 percent, elevation of urinary

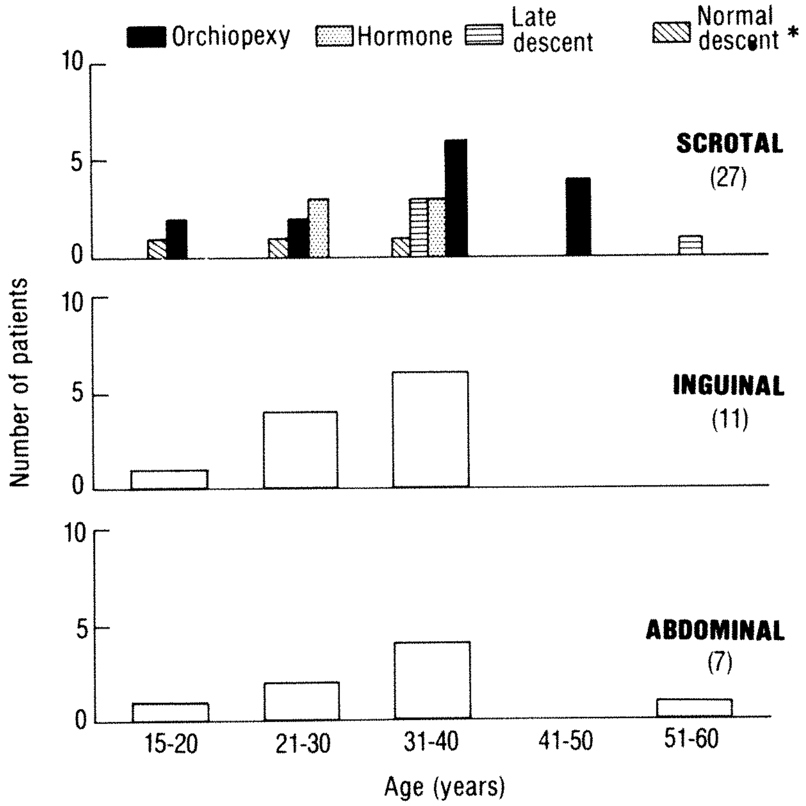

Fig. 1. Age distribution according to tumor location.

* Contralateral historical or current cryptorchidism.

chorionic gonadotropin titers in 16 percent, and unilateral ureteral displacement on excretion urography in nine percent of cases.

SURGICAL-PATHOLOGIC FINDINGS

The left testis was involved in 26 patients and the right testis in 19 patients. The tumorous testis was located in the scrotum in 27 patients, in the groin in eleven, and in the lower abdomen in seven patients. The maximum tumor diameter ranged from 2 to 19 cm, with a median diameter of 8 cm in the scrotal, 6 cm in the inguinal, and 10.5 cm in the abdominal testes. The latter were located between the renal vessels and lower pelvis, and testicular or paratesticular structures were recognized in the operative specimens including a strangulated tumorous testicle medial to the cecum. In two patients, the tumorous inguinal undescended testis was discovered at herniorrhaphy.

Nineteen tumors showed no gross nor microscopic evidence of regional or distant metastases (Stage 1). Involvement of para-

Table II

AGE AT REPAIR AND AT TUMOR DETECTION WITH INTERVAL (LATENT PERIOD) IN-BETWEEN

	Orchiopexy (15 cases)	Hormone (6 cases)	Late Descent (4 cases)	All Repaired Cases (25)
Age At Repair				
Range	4–27	6–11	8–13	4–27 yr.
Median	12	9	11	11 yr.
Age At Tumor				
Range	15–46	21–39	24–60	15–60 yr.
Median	34	30	30	34 yr.*
Interval				
Range	4–33	11–30	16–47	4–47 yr.
Median	19	23	19	20 yr.

* Same as in 20 unrepaired cases.

aortic or pelvic lymph nodes without distant metastases (Stage II) was found in eleven tumors,* by regional lymph node dissection (five) or biopsy (two), or by lymphangiography (four). Distant spread (Stage III) in 15 tumors was noted in the lung (eight) or mediastinum (three) on chest roentgenograms, in the liver or bowel (two) at laparotomy, and in inguinal lymph nodes (two) removed by block dissection.

Histologic examination showed 18 pure seminomas; 17 embryonal carcinomas either alone (eleven), with seminoma (four), or with choriocarcinoma (two); nine teratocarcinomas (teratoma with embryonal carcinoma); and one reticulum cell sarcoma. Lymphocytic infiltration throughout the tumor was observed in two seminomas and one embryonal carcinoma. Tumor thrombi in veins or lymphatic spaces were noted in two embryonal carcinomas, in one teratocarcinoma, and in the reticulum cell sarcoma.

The repaired cases included ten Stage I, ten Stage II, and five Stage III tumors. The unrepaired cases had nine Stage I, one Stage II, and ten Stage III tumors. Pure seminoma occurred in 30 percent (8/27) of the scrotal tumors and in 56 percent (10/18) of the inguinal or abdominal tumors.

TABLE III

CLINICAL PRESENTATION

Symptoms and Signs	No.*
Testicular, inguinal or abdominal pain	25
Testicular swelling	23
Mass in groin or lower abdomen	14
Unilateral or bilateral cryptorchidism	20
Orchiopexy† scar	15
Atrophic other testis	13
Inguinal hernia or herniorrhaphy scar	4
Bilateral gynecomastia	4
Enlarged inguinal lymph nodes	3
Enlarged neck lymph nodes	2
Lesion on chest roentgenograms	11
Regional lymphadenopathy on lymphangiography	8
Positive urinary chorionic gonadotropin	7
Ureteral displacement on excretion urography	4

* Patients usually had more than one symptom or sign.

† Concomitant herniorrhaphy in 4.

TABLE IV

INITIAL TREATMENT

Treatment Methods	No.
Orchiectomy ± lymphadenectomy + radiation therapy	23
Orchiectomy ± lymphadenectomy + chemotherapy	17
Exploration + radiation therapy ± chemotherapy	3
Orchiectomy + radiation therapy + chemotherapy	2
Total	45

METHODS OF TREATMENT

All 45 patients underwent surgery, after preliminary diagnosis of a testicular tumor in 36 and lower abdominal tumor or inguinal hernia in nine. Inguinal or abdominal orchiectomy was carried out in 42 patients with (18) or without (24) regional or inguinal lymph node dissection, and three patients had biopsy only of nonresectable intra-abdominal tumors. Fifteen patients underwent bilateral para-aortic with ipsilateral pelvic lymph node dissection (13) or unilateral or bilateral inguinal lymphadenectomy (two), within three weeks from orchiectomy. External irradiation was delivered to the regional lymphatics in 28 patients; after orchiectomy alone in 22, after orchiectomy plus regional or inguinal lymphadenectomy in three, and after exploratory laparotomy in three patients (Table IV). Systemic chemotherapy was administered in 20 patients following either orchiectomy and lymphadenectomy (12) or orchiectomy alone (five), or with radiation therapy after orchiectomy alone (two) or abdominal exploration (one).

RESULTS

FIVE YEAR SURVIVAL

Eleven patients, including nine in the repaired group who had Stage I (seven) or II (two) tumors and two in the unrepaired

TABLE V

HISTOLOGY *versus* STAGE IN REPAIRED AND UNREPAIRED CASES

Histology	Repaired Cases			Unrepaired Cases		
	Stage I	II	III	Stage I	II	III
Seminoma	4*	3*		7*	1*	3
Embryonal carcinoma	2	6*	2	2*		5
Teratocarcinoma	3	1	3			2
Reticulum cell sarcoma	1					
Total	10†	10‡	5	9	1	10‡

* Thirteen 5 year survivors included three (one of each*) repaired and ten (all*) unrepaired cases.
Eleven including nine (7†, 2‡) repaired and two‡ unrepaired cases are alive with follow-up shorter than 5 years.

group who had Stage III tumors, are alive with less than five years' follow-up (Table V). The over-all five year survival rate for all patients as estimated by the product-limit method[17] is 51 percent. Figure 2 displays the survival rates for Stages I, II, and III, combining both repaired and unrepaired cases. There is a decreasing survival rate with increasing stage; the estimated five year survival rates are 89 percent for Stage I and 37 percent for Stage II tumors. Two Stage III patients among 15 are still alive at 2.7 and 2.3 years so that the Stage III five year survival rate cannot be more than 13 percent.

Within Stage I or III (Fig. 3) there seems to be little or no difference between the survival rates of the repaired and unrepaired cases. The five year survival rates as estimated by the product-limit method for Stage I repaired and unrepaired cases are 80 percent and 100 percent, respectively. For Stage III, the five year survival rate for the repaired cases is zero and for the unrepaired cases less than 20 percent. Since Stage II tumors included only one unrepaired case, no comparison with the repaired cases can be made.

The similarly estimated five year survival rates for the unrepaired and repaired groups are 60 percent and 41 percent, respectively. The five year survival according to histologic type is 78 percent in the seminomas and 29 percent in the other tu-

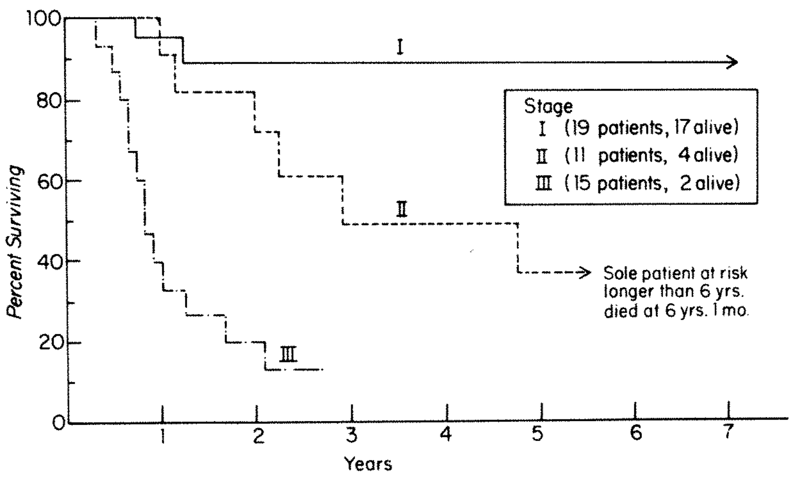

FIG. 2. Survival according to Stage.

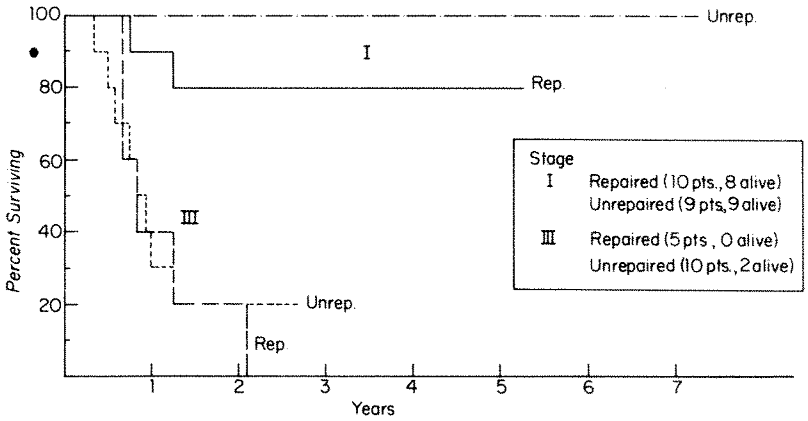

FIG. 3. Survival for Stage I and III repaired and unrepaired cases.

mors. The effect of tumor histology on survival was conspicuous across all stages in both the repaired and unrepaired cases.

Thirteen five year survivors (Table V) included ten unrepaired cases with inguinal (six) or abdominal (four) tumors, and three repaired cases with prior ipsilateral or contralateral orchiopexy or hormonal therapy. These survivors had seminoma (ten) or embryonal carcinoma (three), including three tumors with diffuse lymphocytic infiltration. Fifteen (nine repaired and six unrepaired) cases who initially had gynecomastia, supraclavicular or inguinal lymphadenopathy, positive urinary chorionic gonadotrophin, or vascular tumor thrombi, either were among the non-survivors (twelve) or are alive with less than five years' follow-up (three).

RECURRENCE

All nine Stage I patients in the unrepaired group, including seven who had seminomas and two embryonal carcinomas, survived for more than five years without recurrent tumor after inguinal or abdominal orchiectomy and postoperative external irradiation to the regional lymphatics, including the primary site in the groin (six) or lower abdomen (three). Three of ten Stage I repaired cases developed metastases within one year from treatment; one patient who had a testicular reticulum cell sarcoma died with pulmonary metastases in less than one year after orchiectomy and postoperative irradiation of the regional lymph nodes; another patient with a seminoma died with regional and distant metastases one year after orchiectomy and post operative regional lymphatic irradiation; a third patient who had an embryonal carcinoma underwent wedge resection of a lung metastasis seven months after orchiectomy, regional lymphadenectomy, and postoperative systemic chemotherapy; he is alive and well after three years. The other seven Stage I repaired cases are alive and well after two to six years; after orchiectomy, regional lymphadenectomy, and systemic chemotherapy in four patients who had embryonal carcinomas (two) or teratocarcinomas (two); and following orchiectomy with regional lymphatic irradiation in three patients who had seminomas. One of the latter three patients developed, after five years, a seminoma of the remaining testicle which was then removed by a second orchiectomy and the regional lymphatics were re-irradiated.

Two Stage II patients in the repaired group with pure seminoma and an embryonal carcinoma with seminoma, respectively, are alive and well five years after orchiectomy, and external irradiation of the regional lymphatics in the pure seminoma patient and systemic chemotherapy in the other. Two other Stage II repaired cases, with a seminoma and an embryonal carcinoma on orchiectomy, are alive and well for less than five years following postoperative irradiation and chemotherapy, respectively. Six Stage II repaired cases including four with embryonal carcinomas, one with a seminoma and one with a teratocarcinoma, died with distant metastases in less than five years after orchiectomy with or without regional lymphadenectomy and systemic chemotherapy (three) or regional lymphatic irradiation (three). The one Stage II patient in the unrepaired group, who had a teratocarcinoma, died with distant metastases six years after abdominal orchiectomy and postoperative irradiation of the primary site with adjoining regional lymphatics.

Stage III patients included two in the unrepaired group who are alive and well for less than five years; one who underwent surgical exploration of an inoperable abdominal seminoma with mediastinal lymphadenopathy and was treated by radiation therapy; and the other, who, after an inguinal embryonal carcinoma with choriocarcinoma removed by orchiectomy, underwent regional lymphadenectomy and received chemotherapy for pulmonary lesions which resolved completely. The other 13 Stage III patients, including eight unrepaired cases with initial thoracic (five) or abdominal (two) metastases or inguinal lymphadenopathy (one) and five repaired cases with pulmonary (four) or inguinal (one) metastases, died within two years from treatment with progressive intra-abdominal or extra-abdominal disease.

Of 28 patients treated by postoperative external irradiation to the regional lymphatics, 16 are alive and free of disease; eleven for five or more years and five for less than five years. None of the 16 survivors had block dissection of the regional lymphatics, and all 16 had regional lymphatic irradiation of at least the para-aortic lymph nodes bilaterally and the pelvic lymph nodes on the side of the tumor, including the orchiectomy or laparotomy scar. The radiation doses given ranged from 2,000 rads to 3,500 rads in three to four weeks in 13 patients with seminomas, and from 4,000 rads to 4,500 rads in four to six weeks in three patients with embryonal carcinomas. Table VI indicates that in eleven of twelve patients who developed regional or distant tumor recurrence, limited volumes of regional lymphatics were irradiated or lower radiation doses received, or both, when compared with the 16 nonrecurrent cases.

METASTASES

Initial or subsequent metastases occurred in 18 of 25 patients (75 percent) in the repaired group and in eleven of 20 patients (55 percent) in the unrepaired group. None of the nine Stage I unrepaired cases developed metastases after follow-up periods ranging from nine to 28 years. Thirty percent (3/10) of Stage I repaired cases had distant metastases within one year from treatment. Distant metastases developed, within two years, in 73 percent (8/11) of Stage II repaired (seven) and unrepaired (one) cases.

Of the 29 metastatic cases, three had regional lymph node metastases alone, six had distant metastases alone, and 20 had regional and distant metastases. The distribution of metastases is shown in Table VII. The metastases were intra- and extra-abdominal in 21 patients, only intra-abdominal in five, and only extra-abdominal in three patients. The frequency of metastases was 44 percent (8/18) in seminomas and 78 percent (21/27) in the other tumors.

Involved regional lymph nodes were found: (a) at the time of initial laparotomy in 12 patients, including three with abnormal and one with normal preoperative lymphangiograms; (b) only on abnormal lymphangiograms in five or excretion urograms in two; (c) on subsequent laparotomy in two; and (d) only at autopsy in two patients. Of these 23 patients, 17 had para-aortic and six had para-aortic and pelvic lymph nodal involvement. The metastatic

TABLE VI

RADIATION THERAPY PROCEDURE *versus* TUMOR RECURRENCE

Radiation Procedure	Seminoma (17 cases)		Other Tumors (11 cases)	
	No. Treated	No. Recurred*	No. Treated	No. Recurred†
Volume of irradiated regional lymphatics				
Adequate	13	1	8	5
Inadequate	4	3	3	3
Tumor dosage				
Below 2,000 rads in 2 weeks	1	1		
2,000–3,500 rads in 3–4 weeks	16	3	5	4
4,000–4,500 rads in 4–6 weeks			6	4

Four* and eight† cases, respectively.

lymph nodes were on the same side as the primary tumor in 14 and were bilateral in nine.

Lymphatic metastases, regional or distant, occurred in 24 patients (Table VIII) including three who had only para-aortic lymphadenopathy, and seven who had para-aortic lymphadenopathy and distant metastases other than lymphatic. Of the other 14 patients who also had distant metastases, 13 had para-aortic and other lymphatic metastases including pelvic, and one patient had mediastinal without para-aortic lymphadenopathy.

DISCUSSION

The literature indicates that a testicular neoplasm is more prone to occur in a patient with an undescended testis or with a prior history of cryptorchidism.[1–34] This is consistent with the fact that testicular cancer developed in 25 historically and 20 currently cryptorchid cases registered at Memorial Hospital. Three of these 45 pa-

TABLE VII

SITES OF METASTASES

Intra-abdominal	No.*	Extra-abdominal	No.*
Para-aortic lymph nodes	23	Lung	20
Liver	13	Mediastinal lymph nodes	10
Pelvic lymph nodes	6	Neck lymph nodes	8
Bowel	4	Bone	7
Kidney	4	Inguinal lymph nodes	5
Peritoneum	3	Axillary lymph nodes	5
Inferior vena cava†	3	Pleura	4
Aorta†	2	Brain	2
Iliac vessels†	2	Heart	2
Diaphragm	2	Orchiectomy scar	1
Renal vein†	1	Skin	1
Inferior mesenteric artery†	1	Chest wall	1
Pancreas	1	Spinal cord	1
Adrenal	1	Thyroid	1
Spleen	1	Pituitary	1

* Patients usually had more than one site involved.
† Local tumor involvement.

TABLE VIII

DISTRIBUTION OF LYMPHATIC METASTASES ACCORDING TO TUMOR LOCATION

Involved Lymph Nodes	No.*	Location of Testicular Cancer		
		Scrotum (27 cases)	Groin (11 cases)	Abdomen (7 cases)
Para-aortic	23	16	5	2
Mediastinal	10	7	1	2
Supraclavicular	8	7		1
Pelvic	6	3	1	2
Inguinal	5	4	1	
Axillary	5	4		1
Total	24	17†	5	2

* Patients usually had more than one group of lymph nodes involved.

† Includes eight surgically repaired cases.

tients had cancer of a normally descended testis with contralateral historical or current cryptorchidism, an association that also has been emphasized.[10,14,16,24]

An altered environment, hormonal imbalance, and testicular dysgenesis or atrophy have been implicated as possible oncological factors.[14,16,29] However, repair of the cryptorchid state, at ages four to 27 years, was not helpful in preventing malignancy of the testicle in 25 historical cryptorchids. The interval between repair and tumor detection averaged 20 years, whether repair was spontaneous, by orchiopexy, or by hormonal therapy. The median age at the time of tumor detection was the same (34 years) in the 25 repaired cases as in the other 20 clinically cryptorchid (unrepaired) cases, indicating that repair did not influence the age at which the tumors developed.

The peak incidence, as in testicular cancer in general, was in the fourth decade of life whether the cancerous testis is located in the abdomen, groin, or scrotum and irrespective of modes of correction (Fig. 1). Therefore, carcinogenesis does not seem to be hastened in undescended or maldescended testicles, suggesting that tumor development is independent of testis site *per se*. The point to be emphasized, however, is that concern about the cryptorchid testis does not end following late descent or placement of the testicle in the scrotum. Proper management necessitates careful observation of these patients at regular intervals thereafter.

The initial investigations including laparotomy showed a high incidence of regional or distant metastases, which occurred in 60 percent (15/25) of repaired cases and in 55 percent (11/20) of unrepaired cases. Nevertheless, the estimated over-all five year survival (51 percent) in this series of historical or current cryptorchids approaches that of testicular cancer in general.[19]

The analogous five year survival rates in the repaired *versus* the unrepaired cases according to stage (Fig. 2; and 3) indicate that the prognosis in both groups is determined primarily by the initial anatomical stage of testicular cancer rather than by historical or current evidence of cryptorchidism. The five year survival in the unrepaired (60 percent) and repaired (41 percent) cases correlated with more pure seminomas (11/20:55 percent) in the unrepaired group *versus* more of the other tumors (18/25:72 percent) in the repaired group. The decreasing survival with increasing stage in both groups was also associated with increasing incidence of tumors other than pure seminoma (Table V). The estimated five year survival was 78 percent in the pure seminomas and 29 percent in the other tumors.

Regional lymph node metastases were found initially or subsequently in 56 percent (14/25) of the repaired group and in 45 percent (9/20) of the unrepaired group. Distant metastases were detected on admission in 50 percent (10/20) of the unrepaired cases, and subsequently within two years from treatment in 40 percent (10/25) of the repaired cases. Regional lymphadenopathy preceded, accompanied, or succeeded distant metastases in most (23/29) of the metastatic tumors. Twenty-three patients who initially received external irradiation to the regional lymphatics (16) and/or systemic chemotherapy (seven) are alive without evidence of recurrent tumor for periods ranging from two to 28 years after orchiectomy or abdominal exploration, with or without regional lymph node dissection.

The results here reported suggest the necessity of external irradiation of the regional lymphatics and systemic chemotherapy in the treatment of testicular cancer associated with historical or current cryptorchidism. A previous report[11] includes the various chemotherapeutic agents used in this group of patients. External megavoltage irradiation of the regional lymphatics should encompass the entire bilateral para-aortic area and at least the ipsilateral pelvic region including the primary site in the abdomen or groin. The radiation dosage should be in the range of 2,500 to 3,000 rads in two and one-half to three weeks in pure seminomas and 4,000 to 4,500 rads in four to six weeks in the other tumors. Limiting the irradiated volume or lowering the given radiation dose (Table VI) may result in regional or local recurrence usually associated with distant spread. Likewise, with involved regional (para-aortic and pelvic) lymph nodes especially in seminoma, lack of further irradiation to the mediastinum, the supraclavicular and the groin lymphatics, was associated with recurrent or persistent disease in the lymph nodes above the diaphragm or in the groin in ten patients, nine of whom failed to survive.

CONCLUSIONS

Testicular cancer associated with cryptorchidism occurred whether the cryptorchid state was corrected or not in 45 patients. Patients with a historical or current evidence of cryptorchidism should be observed closely for early detection of cancer and, hence, cure.

Tumor type and anatomic stage are reliable prognostic indices whether the tumorous testis is in the abdomen, groin, or scrotum. The estimated five year survival for Stage I cases was 89 percent after orchiectomy and regional lymphatic irradiation. Less favorable prognoses were recorded with more advanced stages, 80 percent mortality with regional or distal metastases. Routine irradiation of the regional lymphatics and systemic chemotherapy according to histologic type have probably contributed to survival in such patients.

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EFFECT OF THERAPEUTIC IRRADIATION ON THE IMMUNE RESPONSES*

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ABSTRACT:

The immune responses of 60 patients undergoing therapeutic irradiation were evaluated according to four anatomical sites irradiated. *In vitro* lymphocyte transformation tests with PHA, Con-A, and PWM and quantitative assays of IgG, IgA, and IgM were performed on blood obtained from each patient before and during therapy, and two weeks, two months, and six months after therapy. At these same testing intervals, skin tests with PPD, mumps antigen, Candida antigen, and SD-SK were performed.

During irradiation, the mean values of all lymphocyte transformation tests were depressed, varying from 48 percent to 64 percent of pretreatment baseline. This depression persisted until about two months after completion of treatment. By six months, response rose to pretreatment values. When response was evaluated according to sites irradiated with all mitogens, the pelvic and pelvic plus abdominal groups showed consistently greater depression than the chest or head and neck groups. Radiation effected no significant changes in the mean values of IgG, IgA or IgM. A decrease in skin sensitivity was noted during radiation; 73 percent of the subjects responded positively before therapy while only 53 percent had at least one positive test during therapy. By two months postirradiation, 73 percent of the group clinically free of disease had positive skin tests.

A comparison of clinical condition with test results is significant when one considers the 17 patients who developed metastatic disease or died from disease. The depression for all three mitogens during radiation therapy was greater for this group. Of the 17, only four had IgG levels in the normal range, and consistently fewer positive skin tests were demonstrated.

THE role of immunologic factors in the development and course of human malignancy has been extensively studied, and evidence now indicates that an impaired cellular immunity may affect the clinical response and prognosis of cancer patients.[5,9,10,14,17] This cell-mediated response has been measured by the *in vitro* reaction of lymphocytes to various mitogens and by the *in vivo* delayed hypersensitivity response to common skin testing antigens.

If the host's immune status is important in its defense against cancer, it is imperative that the varying effects of treatment modalities on the immune system be evaluated. This study was designed to determine the extent and duration of changes in the general immune responses of human cancer patients receiving therapeutic irradiation.

MATERIAL AND METHOD

Subjects:

Sixty patients, 13 male and 47 female, undergoing radiation therapy were included for evaluation. Their ages ranged from 23 to 82 years, with a mean age of 59 years. They were divided into four major groups according to sites irradiated (Table 1).

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TABLE I

SUBJECT DISTRIBUTION

Site	Total	Male	Female	Mean Age	Dose Range (rads TD)
Head and Neck	13	7	6	61	5–7,000
Oropharynx 1					
Nasopharynx 3					
Hypopharynx 2					
Larynx 1					
Brain 3					
Orbit 3					
Chest	23	0	23	56	5–6,000
Breast 21					
Lung 1					
Thymus 1					
Pelvis Only	18	6	12	65	4–7,000
Vagina 2					
Endometrium 5					
Cervix 4					
Rectum 2					
Prostate 4					
Bladder 1					
Pelvis and Abdomen	6	0	6	48	2,500 strip+ 2,000 pelvic boost
Ovary 5					
Stomach 1					
Total	60	13	47		

Irradiation doses (tumor dose) ranged from 4,000 to 7,000 rads in four to seven weeks in the head and neck group, 5,000 to 6,000 rads in five to seven weeks in the chest group, 4,000 to 7,000 rads in four to seven weeks in the pelvic group, and 2,500 rads using strip technique in the pelvis plus abdomen group. All but one patient in this last group, with carcinoma of the stomach, received an additional boost of 2,000 rads in two weeks to the total pelvis.

Experimental Design:

Blood analyses were made on each patient before and during therapy, and two weeks, two months, and six months after therapy. These included: (1) *in vitro* lymphocyte transformation tests with phytohemagglutinin (PHA), concanavalin-A (Con-A), pokeweed mitogen (PWM) and streptolysin O (STLO); (2) quantitative assays of IgG, IgA, and IgM using radial diffusion technique (Kallestad Kits); and (3) absolute lymphocyte counts.

For lymphocyte transformation tests, heparinized blood was used. Separation of lymphocytes was achieved by a Ficoll-Hypaque gradient.[2] Triplicate cultures were set up in minimum essential medium with and without the mitogen and incubated in a carbon dioxide incubator at 37° C for three days. Tritiated thymidine was then added to each culture and incubated overnight. The unincorporated tritiated thymidine was removed by washing the culture with five percent trichloroacetic acid. The culture was finally counted in a liquid scintillation counter. The blastogenic activity was based on uptake of tritiated thymidine.

Skin tests with purified protein derivative (PPD), mumps antigen, Candida antigen, and streptodornase-streptokinase (SD-SK) were performed at the same testing intervals. An indurated reaction of 5 mm in diameter or greater was considered positive.

RESULTS

Lymphocyte Transformation Tests:

Forty-seven of the 60 (78 percent) subjects showed depressed responses to PWM during radiation therapy as compared to 39 of the 60 (65 percent) showing depression to PHA and Con-A. Figure 1 shows the mean changes of PHA, Con-A, and PWM of the 60 subjects as compared to baseline values before radiation therapy. The significant depression, varying from 48 percent to 64 percent during radiation, persisted until about two months after completion of treatment. The rise in PHA response to 48 percent above pretreatment baseline was observed at the six month testing interval. The results with streptolysin O were not consistent and are not included in this evaluation.

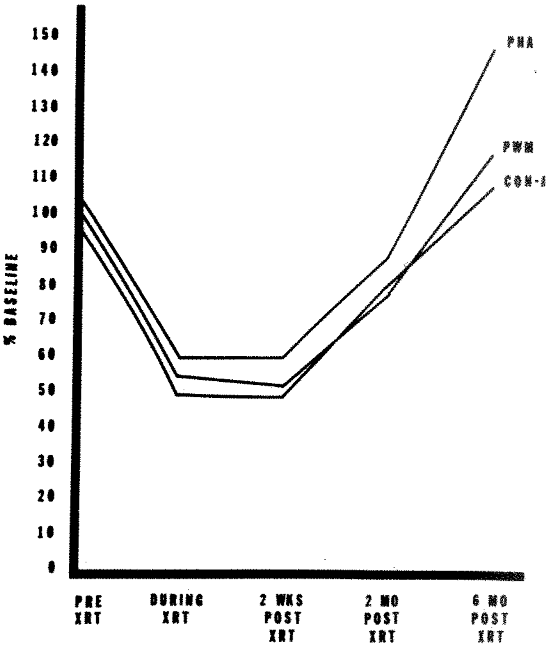

Fig. 1. Changes in PHA, Con-A, and PWM responses with respect to baseline values before radiation therapy.

Skin Tests:

Results with skin tests are shown in Table II. Forty-four of the 60 (73 percent) subjects had positive reactions to at least one antigen before radiation therapy. Positive skin tests dropped to 53 percent during radiation therapy. During radiation therapy, positive skin tests decreased with all patients except the head and neck group.

Test Results Based on Sites Irradiated:

Head and neck group. Figure 2 shows the test results of subjects irradiated in the

Table II

POSITIVE SKIN TESTS AT FIVE TESTING INTERVALS

Testing Interval	All Groups	Head and Neck	Chest	Pelvis Only	Pelvis and Abdomen
Before therapy	44/60* (73 percent)	9/13 (69 percent)	19/23 (83 percent)	12/18 (67 percent)	4/6 (67 percent)
During therapy	32/60 (53 percent)	10/13 (77 percent)	11/23 (48 percent)	9/18 (50 percent)	2/6 (33 percent)
2 weeks after therapy	32/60 (53 percent)	9/13 (69 percent)	11/23 (48 percent)	10/18 (56 percent)	2/6 (33 percent)
2 months after therapy	38/57 (67 percent)	8/13 (62 percent)	15/21 (71 percent)	13/18 (72 percent)	2/5 (40 percent)
6 months after therapy	27/46 (59 percent)	6/12 (50 percent)	11/15 (73 percent)	9/15 (60 percent)	1/4 (25 percent)

* Number with positive tests/total number of subjects tested.

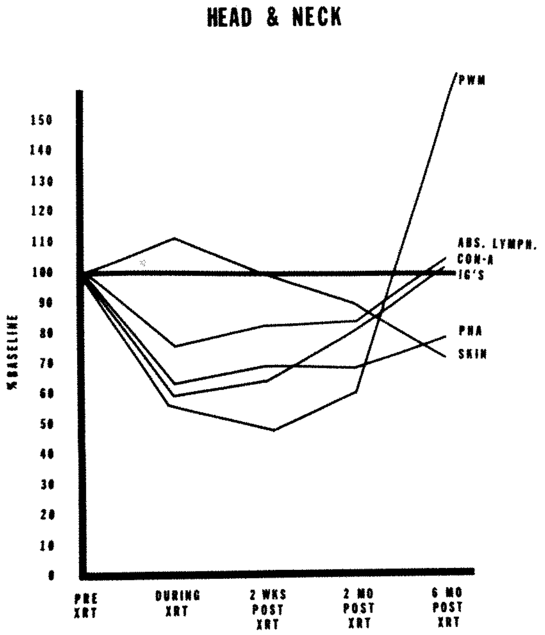

FIG. 2. Changes in absolute lymphocyte counts, skin test results, PHA, Con-A, and PWM responses with respect to baseline values in head and neck group.

head and neck region with respect to the baseline values determined before radiation therapy. The mean values of immunoglobulins (Ig's) were not significantly affected by irradiation. All mean values were within the normal ranges: 1,000–1,500 mg per 100 ml for IgG, 100–400 mg per 100 ml for IgA, and 60–180 mg per 100 ml for IgM. Skin tests were unchanged during head and neck irradiation. A drop in positive skin tests occurred at two and six months; two of these subjects developed early metastatic disease.

Before radiation therapy, the mean absolute lymphocyte count for this group of subjects was 2,046 per mm^3. During radiation therapy, the mean dropped to 1,558 per mm^3 or 76 percent of the baseline value. The mean values at two weeks, two months, and six months postirradiation were 1,671, 1,719, and 2,120 per mm^3 or 82 percent, 84 percent, and 104 percent of the baseline value, respectively. Significant depression of PHA, Con-A and PWM responses was noted during irradiation; the greatest depression observed was with PWM at two weeks postirradiation. At six months, the mean values for PHA, Con-A and PWM responses were 79 percent, 102 percent, and 176 percent of the baseline values, respectively.

Chest group. Results of parameters used to measure immune response in patients receiving irradiation to the chest are shown in Figure 3. No significant changes were noted with the immunoglobulins (Ig's); however, significant depression was noted with all other test parameters during irradiation. The mean absolute lymphocyte count for this group of subjects before radiation therapy was 1,854 per mm^3. The mean value dropped to 870 per mm^3 or 47 percent of the baseline during irradiation and returned to 1,470 or 79 percent of the baseline at six months. The mean values for PHA, Con-A and PWM responses at six months were 122 percent, 102 percent, and 74 percent of the baseline values, respectively.

Pelvis group. Changes in test parameters of patients receiving irradiation to the

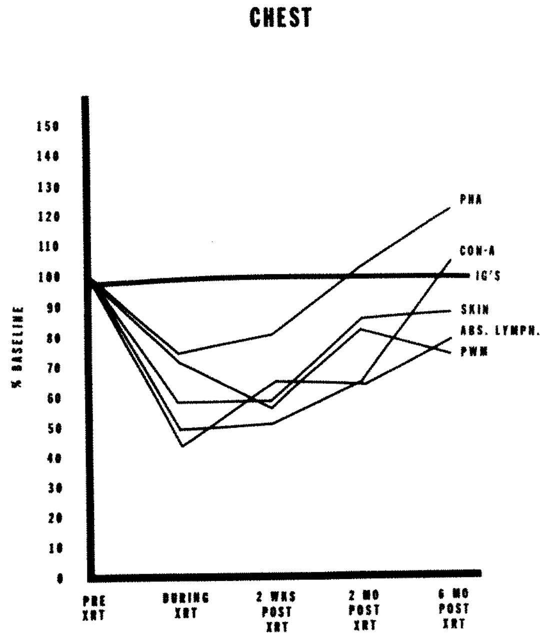

FIG. 3. Changes in absolute lymphocyte counts, skin test results, PHA, Con-A, and PWM responses with respect to baseline values in chest group.

pelvis only are seen in Figure 4. The mean absolute lymphocyte count for this group before radiation therapy was 1,691 per mm^3. Significant depression was noted with skin test results, absolute lymphocytes, PHA, Con-A, and PWM responses both during and postirradiation. At six months, the mean values of both PWM and PHA responses rose above the baseline values, while the value for Con-A response remained below baseline. A drop in positive skin tests and mean absolute lymphocytes was noted at six months.

Pelvis and abdomen group. Patients receiving irradiation to the whole pelvis and abdomen are summarized in Figure 5. The mean absolute lymphocyte count before radiation therapy was 1,500 per mm^3. Significant depression was noted with all the test parameters except immunoglobulins (Ig's) during and after irradiation. The depression in PHA, Con-A and PWM responses was both extensive and persistent with this group of subjects. A drop in positive skin tests was noted at six months.

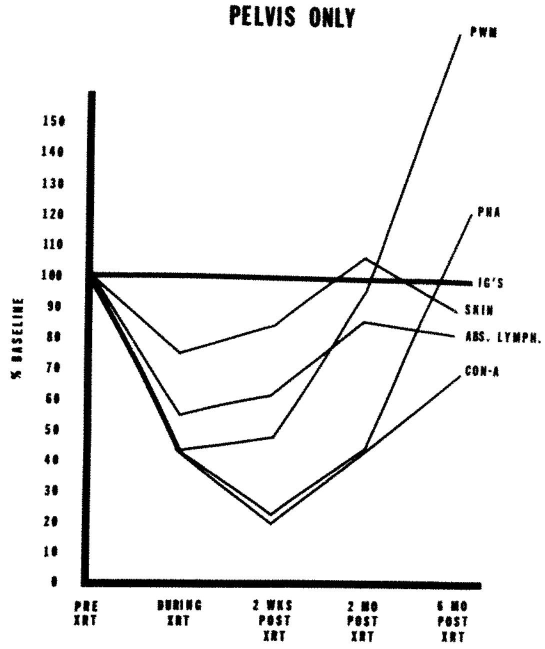

Fig. 4. Changes in absolute lymphocyte counts, skin test results, PHA, Con-A, and PWM responses with respect to baseline values in pelvis group.

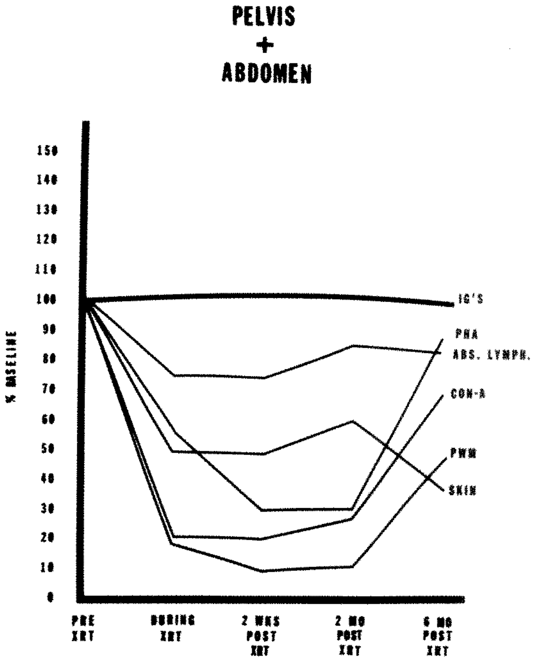

Fig. 5. Changes in absolute lymphocyte counts, skin test results, PHA, Con-A, and PWM responses with respect to baseline values in pelvis and abdomen group.

Relation of Tests to Clinical Status:

During the first year follow-up, 17 subjects developed metastatic disease or died from their disease. Although no significant changes were effected by irradiation for the mean values of IgG, IgA or IgM, individual analyses revealed that eight of these 17 subjects (47 percent) who developed metastatic disease or died during the first year follow-up had significantly elevated IgG levels at last testing intervals. The IgG levels ranged from 1,800–3,000 mg per 100 ml. In comparison, only four of 43 subjects judged clinically to be without evidence of disease had IgG levels in this elevated range (Table III). Twelve of the 60 subjects had subnormal IgG in the range of 265 to 850 mg per 100 ml at the last testing intervals, and of the twelve, four developed metastatic disease or died during the first year follow-up.

Table IV compares the lymphocyte transformation and skin test results with the

TABLE III

COMPARISON OF IgG LEVEL WITH CLINICAL CONDITION*

Clinical Condition	Number of Subjects			
	Total	IgG Levels		
		High	Low	Normal
No Evidence of Disease	43	4 (1,800–2,600)†	8 (420–850)	31
Metastasis	17	8 (1,800–3,000)	4 (265–640)	5
Total	60	12	12	36

* $p < 0.01$.
† Range of IgG in mg/100 ml.

clinical condition. The mean values for PHA and Con-A responses for the group who developed metastatic disease or died from disease were lower than those for the subjects without evidence of disease at the testing interval prior to radiation therapy. Also, the depressions for all three mitogens following radiation therapy were greater for the group of subjects who developed metastatic disease or died from disease. The percentage of positive skin tests prior to radiation therapy did not differ in the two groups; however, the group with poor prognosis had consistently fewer positive tests during all the four other testing intervals. Table v shows the PHA and skin test results of these 17 subjects prior to metastasis or death. Of the ten subjects who developed metastasis or died within five months after radiation therapy, eight had depressed PHA responses and all had negative skin tests. Of the seven subjects who died between eight and 13 months after radiation therapy, only one had depressed PHA response and three had negative skin tests.

DISCUSSION

In vitro lymphocyte transformation tests with PHA and Con-A have been used by various investigators for measuring the function of thymus-derived or T-lympho-

TABLE IV

COMPARISON OF LYMPHOCYTE TRANSFORMATION AND SKIN TEST RESULTS WITH CLINICAL STATUS

Testing Intervals	Mean Values of Lymphocyte Response CPM $\times 10^3$						Percent with Positive Skin Tests	
	PHA		Con-A		PWM			
	NED*	M–D†	NED	M–D	NED	M–D	NED	M–D
Before therapy	108 (43)‡	79 (17)	34 (42)	21 (18)	19 (43)	18 (17)	77 (43)	76 (17)
During therapy	79 (43)	53 (17)	14 (43)	20 (18)	10 (42)	10 (17)	58 (43)	45 (17)
2 weeks after therapy	78 (43)	49 (15)	19 (43)	6 (17)	9 (42)	6 (16)	63 (42)	40 (17)
2 months after therapy	88 (42)	85 (15)	27 (42)	11 (15)	14 (41)	8 (15)	73 (40)	57 (15)
6 months after therapy	130 (43)	107 (10)	27 (45)	18 (10)	17 (42)	11 (10)	72 (40)	40 (10)

* NED= no evidence of disease; †M-D—metastasis or death. ‡( ) Number of subjects included for evaluation.
PHA= Phytohemagglutinin; Con-A= concanavalin-A; PWM= pokeweed mitogen.

cytes and the response to PWM for the function of bursa-derived or B-lymphocytes. This study of 60 subjects with different tumor types demonstrates that therapeutic irradiation depresses lymphocyte responses to all three mitogens, suggesting that the function of both the B- and T-lymphocytes may have been affected at the same time. Of the 60 subjects studied, 65 percent showed depressed responses to PHA and Con-A, and 78 percent showed depression to PWM during radiation therapy. Our data thus suggest that radiation affected the B-cell population more than the T-cell. The study of Stjernswärd *et al.*,[15] using PHA along with B- and T-cell markers, indicated that only the T-cells were largely eliminated by irradiation in patients with breast carcinoma. Studying patients with carcinoma of the bronchus, Braeman[3] reported depression of PHA but not of PWM response following radiation therapy. The differences between our findings and those of the previous reports may be attributed to technique sensitivity, treatment technique, etc.; nevertheless, studies with animals have shown that T-lymphocytes are more radioresistant than the B-lymphocytes.[11] Our follow-up data demonstrated that in the majority of subjects, the depressed *in vitro* responses persisted for about two months. A significantly higher response to PWM and PHA at six month follow-up (Fig. 1–4) suggests an enhanced activity of both the B- and T-lymphocytes following radiation therapy. Other investigators have also observed enhanced humoral and cell-mediated immune response following irradiation.[6–8] Irradiation involving pelvis only and pelvis plus abdomen showed greater depression to the lymphocyte transformation tests than the other two sites irradiated. This may be due to the greater volume of lymphoid and marrow tissue being irradiated.

TABLE V

PHA AND SKIN TEST RESULTS OF 17 SUBJECTS PRIOR TO METASTASIS (M) OR DEATH (D) DURING FIRST YEAR FOLLOW-UP

Tumor Location	Clinical Condition	PHA	Skin Tests
Breast	D 1 mo.*	↓	Neg.
Breast	D 2 mo.	↓	Neg.
Ovary	D 2 mo.	↓	Neg.
Prostate	D 2 mo.	↓	Neg.
Nasopharynx	M 2 mo.	OK	Neg.
Ovary	D 3 mo.	↓	Neg.
Breast	M 3 mo.	↓	Neg.
Rectum	D 4 mo.	OK	Neg.
Cervix	Recurrence 4 mo.	↓	Neg.
Breast	D 5 mo.	↓	Neg.
Nasopharynx	D 8 mo.	↓	Neg.
Breast	D 9 mo.	OK	Neg.
Rectum	D 9 mo.	OK	Pos.
Lung	D 9 mo.	OK	Pos.
Prostate	D 10 mo.	OK	Neg.
Breast	D 12 mo.	OK	Pos.
Breast	D 13 mo.	OK	Pos.

* After radiotherapy.
PHA = Phytohemagglutinin.

Irradiation did not seem to affect the *in vivo* skin response in the head and neck group. Using common skin testing antigens similar to those used in this study, Clement and Kramer[6] did not detect a significant effect of therapeutic irradiation on the cell-mediated immune response in their subjects. However, the change from positive to negative skin tests at two month and six month follow-up (Table II and IV) in subjects with poor prognosis was of interest. Some investigators have suggested the prognostic value of *in vivo* skin tests in cancer patients,[1,12] but others have not found a significant correlation of clinical condition with either the *in vivo* or the *in vitro* tests.[4,16] This study neither supports nor disputes this point. Analysis of 17 subjects who developed metastatic disease or died from disease during the first year follow-up indicates that both the *in vitro* lymphocyte transformation tests and *in vivo* skin tests seemingly measure only the "current" or "on-going" general immune competence. Their inability to predict long-term clinical condition is evidenced by the test results observed in those who died eight to 13 months postradiation therapy, as 43 percent of them had positive skin tests and all except one had normal PHA responses (Table v). In order to better correlate the test results with clinical condition or prognosis, these tests may have to be performed at more close-spaced intervals. Also, to evaluate further the effects of irradiation, tumor cell type, and extent of tumor on the immune response, more subjects in each group must be studied.

Enhanced antibody response following radiation therapy has been previously reported.[7,8] In this study, quantitative assays of immunoglobulins revealed significant increase of IgG in 47 percent of subjects who developed metastatic disease or died from disease, as compared to nine percent of subjects without evidence of disease. This difference is statistically significant; however, the nature of such IgG antibody or antibodies is not known. Some possible explanations for the observed increase of IgG include: (1) stimulation from tumor antigen altered by irradiation;[7] (2) an association with the "blocking factor" described by the Hellströms;[13] and (3) an abnormal increase of antibodies against commonly present infectious agents in the terminal stage of malignancy. More specific assay of such antibodies may be of value here.

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THE SPECTRUM OF OSTEOBLASTOMA*

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ABSTRACT:

Benign osteoblastoma is a rare tumor, more frequent in males, usually occurring in patients under the age of 30 years, and is seen most frequently in the spine, femur, tibia, and mandible. Its varied roentgenographic appearance may suggest a large osteoid osteoma or an aneurysmal bone cyst, but about one-fourth of cases present a picture consistent with a malignant neoplasm. The roentgen changes in the spine are frequently subtle and require care for identification. Differentiation from osteogenic sarcoma is sometimes difficult even with histological material, because some low grade osteogenic sarcomas contain areas resembling osteoblastoma. Conservative surgery is the treatment of choice for osteoblastoma.

BENIGN osteoblastoma is a rare primary neoplasm comprising less than one percent of primary tumors of bone.[3]

Osteoid osteoma and benign osteoblastoma are closely related processes with similar histologic patterns.[2,6,12,13,15] Severe pain, interfering with sleep and relieved by aspirin, is characteristic of osteoid osteomas but may also occur in osteoblastomas. The roentgenographic features of the lesions are occasionally indistinguishable.[14] Perhaps the most significant difference between these two lesions is their size. Osteoid osteomas have a limited growth potential and only rarely exceed 1 cm in diameter; osteoblastomas, however, are often several centimeters in diameter when initially detected.

We classify all lesions less than 1 cm in diameter as osteoid osteomas and all those more than 2 cm as osteoblastomas. Between 1 and 2 cm the differentiation may be difficult (Fig. 1) and we use an arbitrary division point—a diameter of 1.5 cm—in those lesions indistinguishable by all other criteria. Confusing the issue is the occasional lesion satisfying the diagnostic criteria of osteoid osteoma at one stage and later developing into a typical osteoblastoma. This occurred in three cases in our series (Fig. 2; and 3).

This study includes 123 patients with osteoblastoma, 45 of whom were seen at the Mayo Clinic; the other 78 patients were seen in consultation. Roentgenograms or photographs of roentgenograms were available in 74 of the cases. Based on the previously mentioned criteria, 152 other Mayo Clinic cases with a diagnosis of osteoid osteoma were excluded from this study.

CLINICAL FEATURES

The ages of the 87 males and 36 females ranged from three to 70 years (Fig. 4). Nearly 90 percent were less than 30 years old; nearly three-fourths were in the second and third decades.

The cardinal symptom, pain, occurred in 84 percent of the patients and was usually localized to the site of the tumor except when the tumor impinged on adjacent nerve roots or the spinal cord. Although occasionally severe, the pain was more commonly mild and of long duration (average, 17 months). In 13 percent of the patients, the pain was worse at night. Aspirin relieved pain in only seven percent. Also a common finding was localized swelling. Patients with spinal tumors frequently had scoliosis and muscle spasm; neurologic

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From the Mayo Clinic and Mayo Foundation, Rochester, Minnesota.

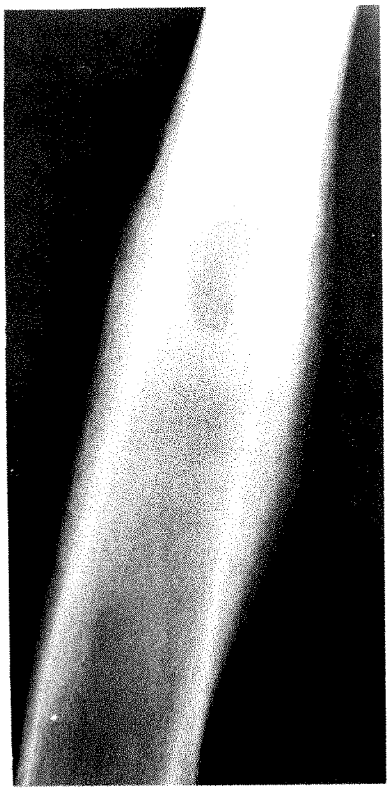

Fig. 1. Osteoid osteoma *versus* osteoblastoma; this 1.4 cm tumor in the midfemur of an 18 year old boy is difficult to classify even with roentgenograms. We favored osteoblastoma, based on histologic pattern.

symptoms were common in this group (26 percent). Disuse atrophy and limp also occurred in lesions in the extremities.

PATHOLOGIC FEATURES

Most benign osteoblastomas are readily diagnosed by the pathologist. The lesion is usually well circumscribed by a layer of periosteum that may be "expanded." The tumor is bloody and usually homogeneously granular or gritty because of its component of mineralized osteoid. Microscopically the tumor is composed of anastomosing trabeculae of osteoid tissue (Fig. 5). The osteoid is mantled by prominent osteoblasts usually with abundant cytoplasm. Nucleoli may be prominent, as in the proliferating osteoblasts of a callus. Consonant with the benign course of the lesion, nuclei are usually regular in size (although they occasionally show considerable variation in size—which may be misleading). Situated among the trabeculae is vascular connective tissue that may even simulate hemangioma. Adjacent to the vessels are a few spindle-shaped cells that, because of their association with collagenous deposition, are probably fibroblasts. The early designation of this lesion was osteogenic fibroma.[10] Osteoclast-like giant cells, although often scattered among the other elements, are not a dominant feature. Large vascular spaces similar to those of aneurysmal bone cysts may be present.

Osteoblastomas of the jaws are well-demarcated tumors often surrounding a root or roots of teeth (Fig. 6); in the literature on oral surgery, such tumors are usually called cementoblastomas.[1,7] Although the abnormal tissue usually consists of rather parallel and radiating trabeculae discretely demarcated from surrounding bone in their periphery (Fig. 7), such findings again may overlap those of osteoblastomas in other sites. Our series included 23 osteoblastomas of the jaw.

Osteoid osteoma in its classic small form consists of a discrete "nidus" of tightly interlacing trabeculae of osteoid, often with small mantling osteoblasts. With good demarcation, this tumor abuts surrounding bony trabeculae that are large and usually moderately or severely sclerotic. Among the tightly woven trabeculae of the nidus are a few fibroblasts and multinucleated giant cells.

For years it has been known that the histopathology of the osteoid osteoma overlaps that of the benign osteoblastoma. Some tumors contain features of both, such as tightly woven and loosely arranged areas. The term "giant osteoid osteoma" was introduced in 1954[4] in an attempt to recognize this by arbitrarily regarding tumors of over a certain size (usually 2 cm in diameter) as different from ordinary osteoid osteomas. Subsequently osteoblastoma[9,11] has become a more generally employed designation than is giant osteoid osteoma for these larger lesions.

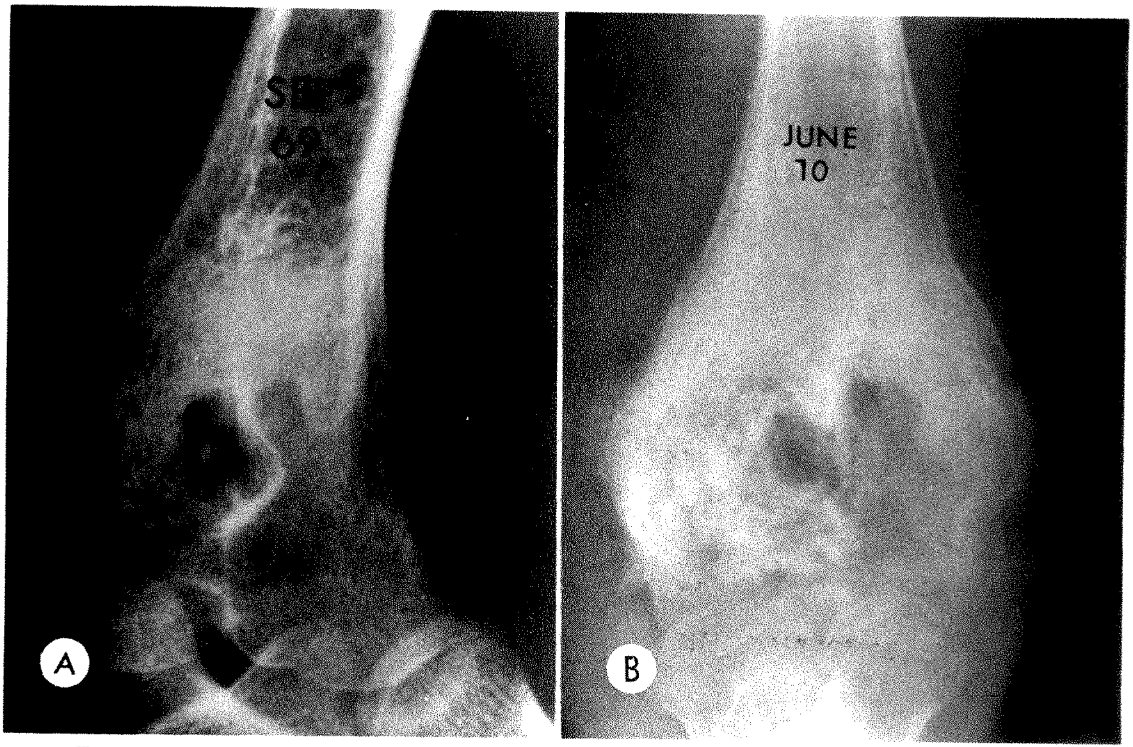

Fig. 2. (*A* and *B*) Transition from osteoid osteoma to osteoblastoma in 14 year old boy with painful lesion in distal humerus. Well without recurrence three years after surgery.

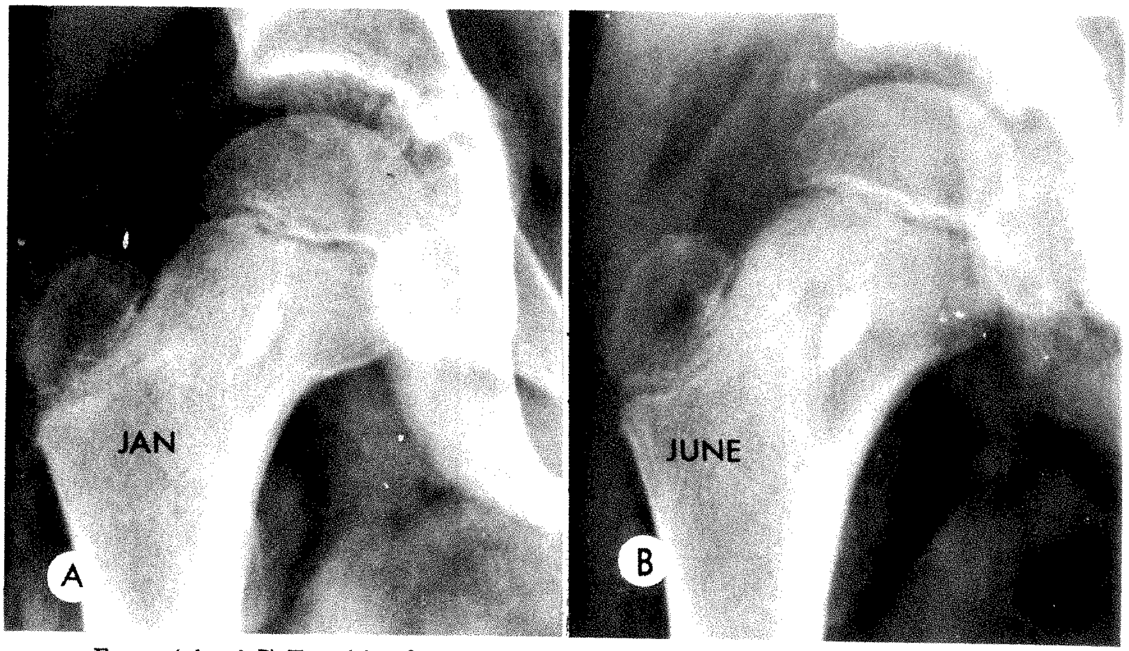

Fig. 3. (*A* and *B*) Transition from osteoid osteoma to osteoblastoma in nine year old boy with hip pain relieved by aspirin. Well three years after curettage.

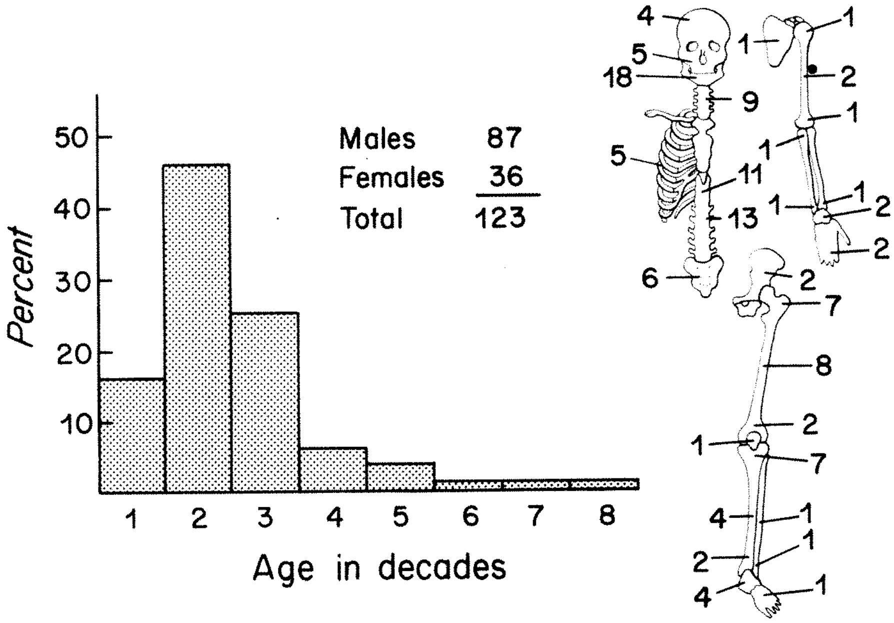

FIG. 4. Age and sex of patients; sites of benign osteoblastoma.

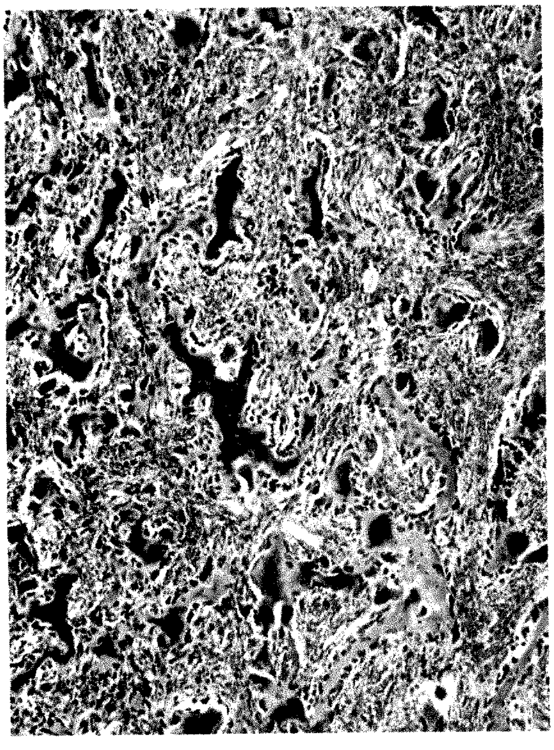

FIG. 5. Classic osteoblastoma with irregular trabeculae of osteoid and bone mantled by benign-appearing osteoblasts. These usually have abundant cytoplasm. Between them is a vascular spindle-cell fibroblastic stroma. Osteoclasts are sparse or fairly abundant. (Hematoxylin and eosin; ×100.)

A few of these lesions, often with the tighter pattern of osteoid osteomas, are multicentric. In those few, the surgical problem of curing the patient becomes more difficult. The patient's pain may persist postoperatively if a tiny nidus is overlooked. In three of our cases, the nidus presented as a wormlike or multifocal zone of small masses measuring up to about 1 cm in diameter in a reactive, discrete mass of nontumorous bone. The largest of these resultant lesions was a periosteally located mass (10 by 6 by 6 cm) on the posterior aspect of a distal femur (Fig. 8). Hence it becomes necessary to recognize, as Schajowicz and Lemos[15] have, that lesions may be: (1) small, like classic osteoid osteomas; (2) large, like osteoblastomas; or (3) multicentric. They also mentioned two cases of probable sarcomatous change in osteoblastomas.

Another feature, the importance of which is unknown, is the fact that osteogenic sarcoma may be well differentiated and quite similar to osteoblastoma. We have seen a case in which obvious osteogenic sarcoma developed during a 3.8 year period in what was originally thought to be

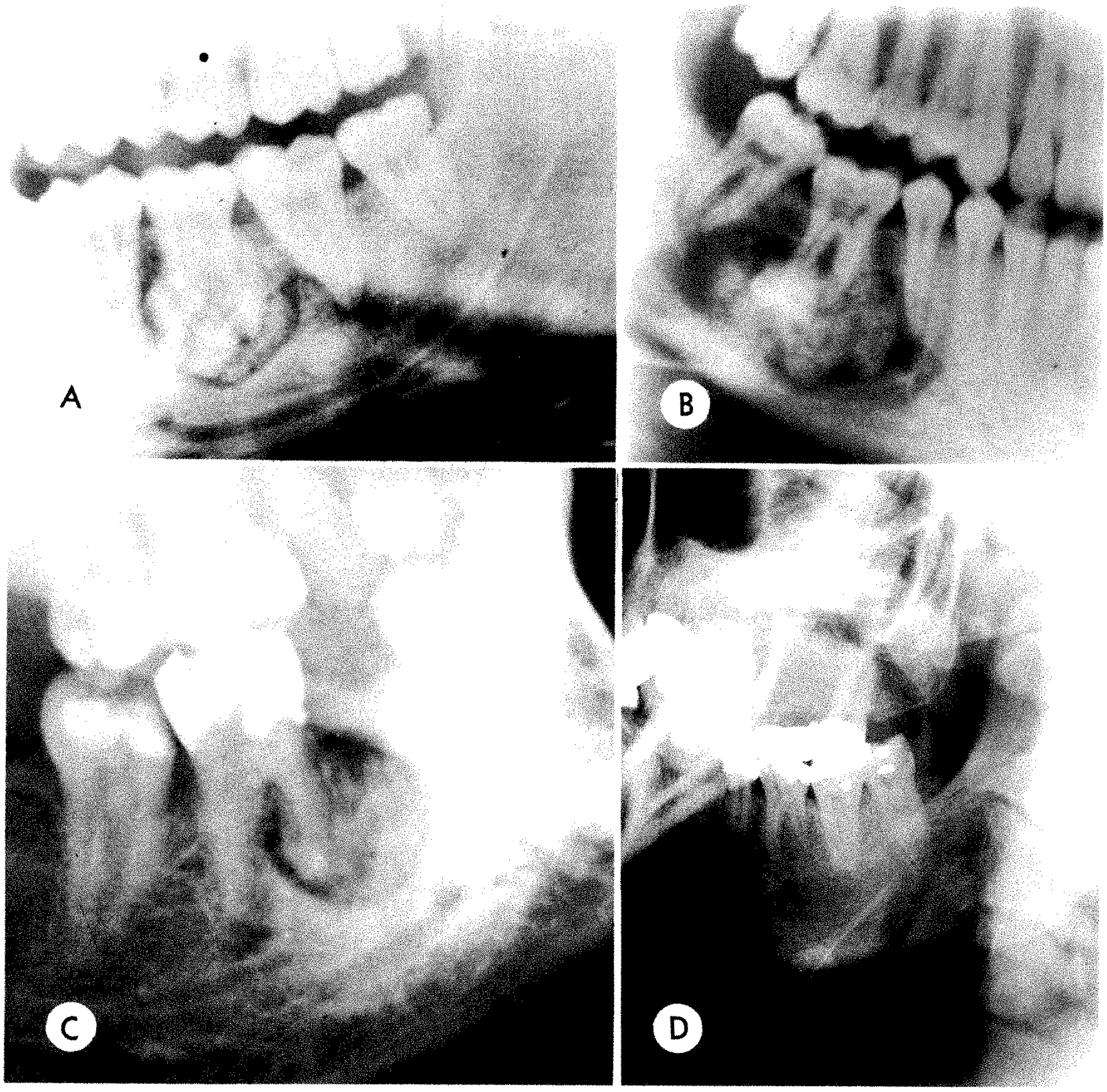

Fig. 6. Osteoblastoma of mandible. (*A*) Heavily mineralized tumor surrounding tooth root in 24 year old man. Note typical radiolucent halo and sharp demarcation. (*B*) Wide radiolucent halo in 13 year old girl, now well without recurrence three years after excision. (*C*) Typical roentgenogram in 26 year old woman who had pain for six months and is now well four years after curettage. (*D*) Totally lucent tumor in 27 year old man who had pain for twelve months and is now without recurrence seven years after excision.

an osteoblastoma of a tibia (Fig. 9); whether or not this tumor was originally malignant is unknown. In another case, osteosarcoma coexisted with benign zones indistinguishable from osteoblastoma. This tumor raises the question, "Did malignancy develop in osteoblastoma or can malignant tumors simulate osteoblastoma?"

The final problem we have observed regarding the pathology is the occasional example of osteoblastoma containing numerous bizarre nuclei consistent with osteosarcoma. These large irregular nuclei are associated with little or no mitotic activity and may result from degenerative change (Fig. 10). In two of the three cases, such lesions were categorized as benign, partly because the roentgenographic defect was considered to be that of a benign lesion; follow-up has confirmed the nonmalignant interpretation.

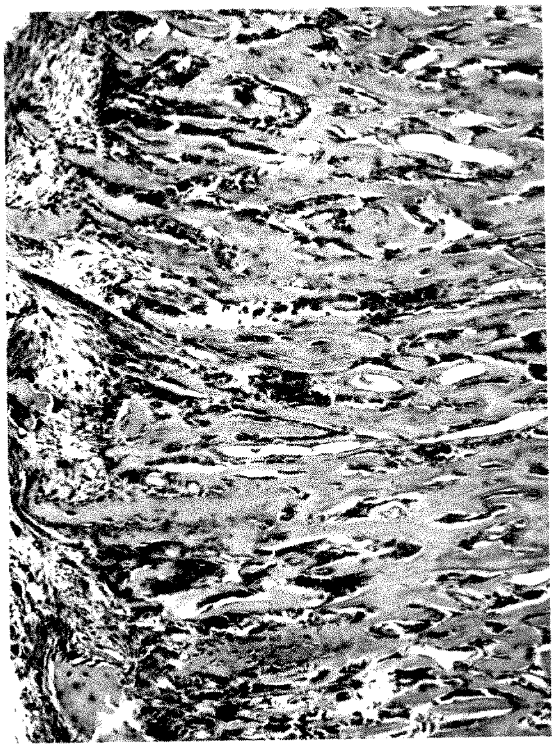

FIG. 7. Periphery of unusual pattern with radiating trabeculae of osteoid and new bone. Although unusual for osteoblastomas generally, this is common at the periphery of osteoblastomas that are associated with the root of a tooth (cementoblastomas). (Hematoxylin and eosin; ×100.)

ROENTGENOGRAPHIC FEATURES

Location. Of the 123 tumors, 39 were located in the spine and 23 occurred in the jaws; the remaining 61 tumors were distributed throughout the appendicular skeleton with a predilection (30 tumors) for the femur and tibia (Fig. 4). Thus, 75 percent of these tumors occurred in the mandible, spine, femur, or tibia. Probably no bone is exempt as a possible location for this tumor; unusual sites included ribs (five), small bones of the hands (Fig. 11) and feet (nine), facial bones (two), calvarium (two), patella (one), scapula (one), and ilium (two).

Appendicular tumors. Of the 61 tumors in this group, roentgenograms of 40 were available (Fig. 12). Sixty percent of the cases were located within the cortex; the remainder were medullary.

Of the tumors that occurred in the long bones, 76 percent were located in the diaphysis. The remaining 24 percent were metaphyseal. No epiphyseal lesions were encountered.

Tumor size at initial clinical presentation was variable, ranging from 0.6 to 7.7 cm (average size, 3.6 cm). Only three lesions were less than 2 cm in diameter. Seventy-five percent of the tumors were either spherical or slightly oval, and the remainder were elongated.

The margin was well defined and distinct in 83 percent of the cases. Occasionally margination cannot be assessed because the tumor is obscured by dense reactive sclerosis in the surrounding bone. This sclerosis may be many times as large as the lesion itself (Fig. 12, *A* and *B*). Half of these appendicular tumors elicited considerable reactive sclerosis in the adjacent bone, 37 percent had no surrounding sclerosis whatsoever, and 13 percent had only a surrounding sclerotic rim.

The interior of the tumor was lucent in 64 percent of the cases and the remainder showed various degrees of ossification. Serial films of several cases suggest that younger lesions tend to be lucent but ossify as they mature. Four tumors exhibited a centrally located ossified nidus, a very helpful finding (Fig. 12*D*).

Approximately three-fourths of the tumors showed cortical expansion, usually eccentric. Expansion was arbitrarily judged to be mild in 29 percent, moderate in 57 percent, and marked in 14 percent. Approximately 80 percent of the tumors had a cortex that was either perfectly normal or intact even though expanded and thinned. Surprisingly, 20 percent showed definite cortical destruction or penetration that suggested a malignant lesion (Fig. 12*F*). Fifty-eight percent showed periosteal new bone formation, which at times was extremely exuberant. These periosteal reactions were of the "benign" solid type in 86 percent; the rest had either spiculation or multilamination that suggested a more aggressive lesion. Trabeculation within the

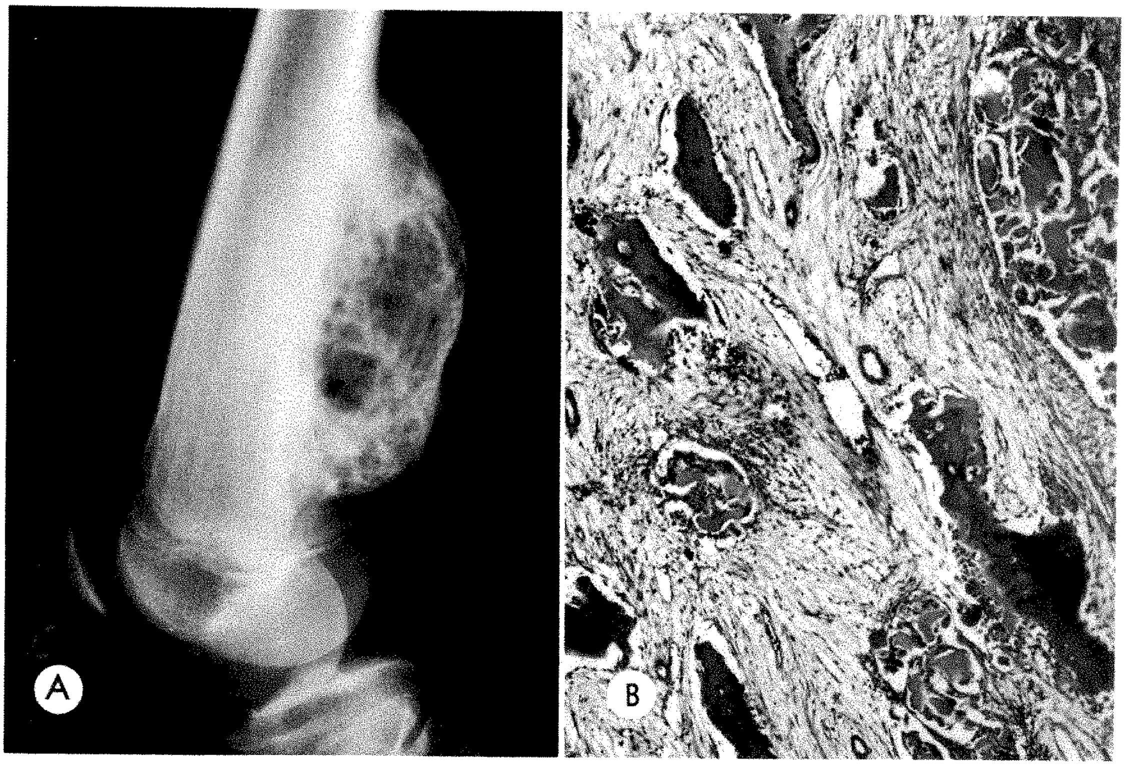

FIG. 8. Multifocal osteoblastoma. (*A*) Roentgenogram of a 17 year old boy shows large, heavily mineralized tumor of distal femur. He is well eight years after surgery. (*B*) Multicentric islands of osteoblastoma separated by trabeculae of non-neoplastic new bone and fibrous tissue. (Hematoxylin and eosin; ×100.)

tumor was seen in only 13 percent of the cases.

Pathologic fracture was rare; it occurred in two children under the age of ten. These two tumors were in the distal radius and the midfemur.

Unfortunately, roentgenographic features of these appendicular lesions suggested osteoblastoma in only 29 percent of the cases. One-third were so non-specific in appearance that a definite diagnosis could not be suggested. Of the remaining 15 cases, five were thought to represent osteoid osteoma, four osteogenic sarcoma, two non-ossifying fibroma, two fibrous dysplasia, and two metastasis. In our opinion, the roentgenographic features were suggestive of a malignant lesion in 25 percent of the cases. All of these were typical osteoblastomas histologically and all had a benign clinical course.

Spinal Tumors.[5,8] Of the 39 tumors in the vertebral column (Fig. 13), nine were cervical, eleven thoracic, 13 lumbar, and six sacral. Involvement of the vertebral body alone was uncommon, occurring in only 14 percent of the cases. Twenty-four percent involved both the body and the dorsal elements. The remaining 62 percent were limited to the dorsal elements. A thoracic lesion in a 56 year old man involved two adjacent vertebrae.

The diameters of these tumors ranged from 1.4 to 10 cm (average, 3.4 cm). The margin was well defined in 68 percent and poorly defined in 23 percent. The remaining tumor margins could not be evaluated because of obscuration by reactive sclerosis. Most commonly the adjacent bone was normal (56 percent) and without reactive sclerosis. Of the remaining 44 percent, half had a surrounding sclerotic rim and half, considerable surrounding sclerosis. The interior of the tumor was lucent in 52 percent

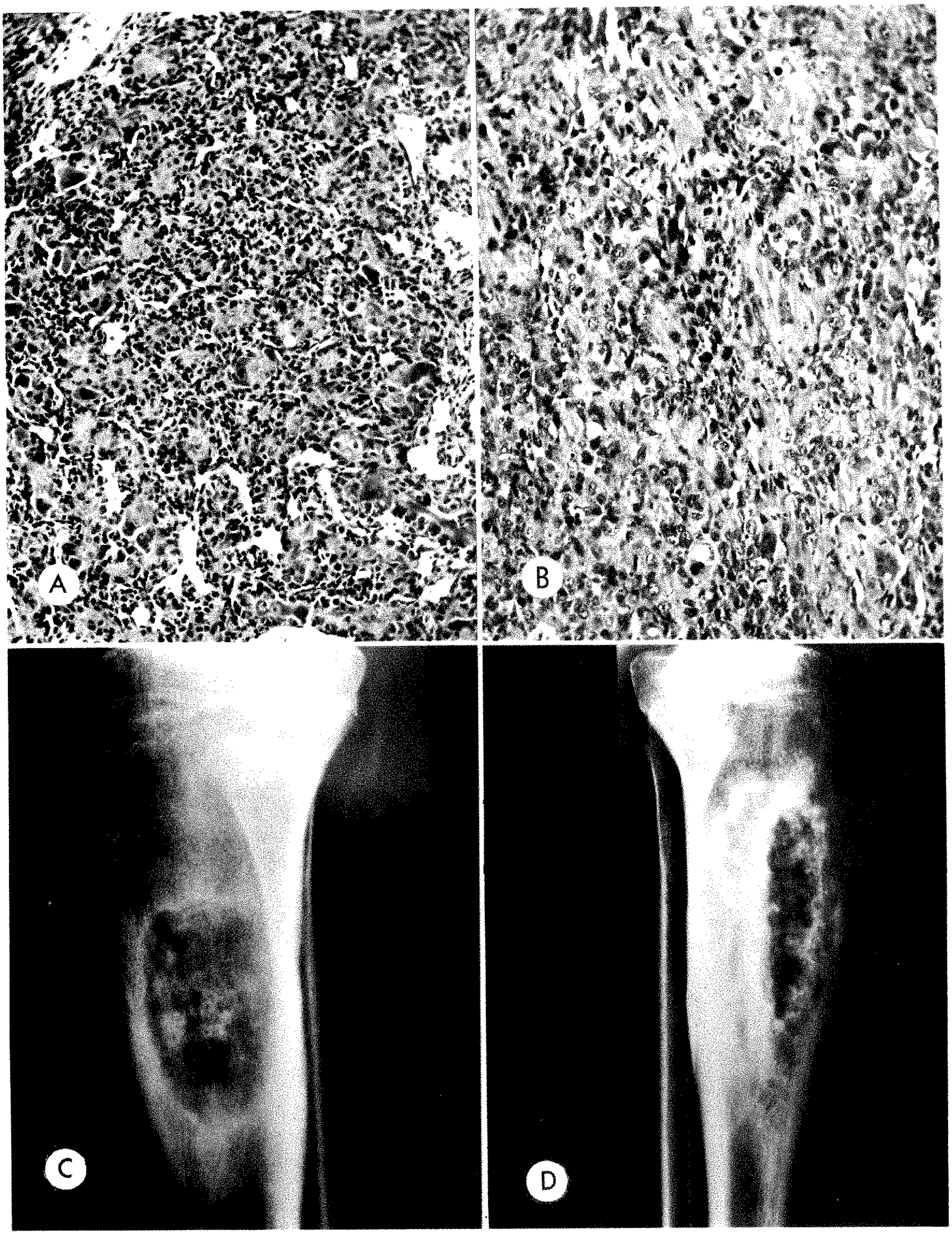

FIG. 9. Osteogenic sarcoma or osteoblastoma? (*A*) Classic osteoblastoma with benign-appearing osteoblasts and more compact stroma between the trabeculae. (Hematoxylin and eosin; ×160.) (*B*) Same patient three and one-third years later. Now obvious osteogenic sarcoma containing hyperchromatic osteoid-producing stromal cells and large nucleoli. The tumor has metastasized. (Hematoxylin and eosin; ×160.) (*C*) Original roentgenogram shows well-defined tumor with mild cortical expansion and ossified matrix compatible with osteoblastoma. (*D*) Roentgenogram three years later shows a malignant lesion.

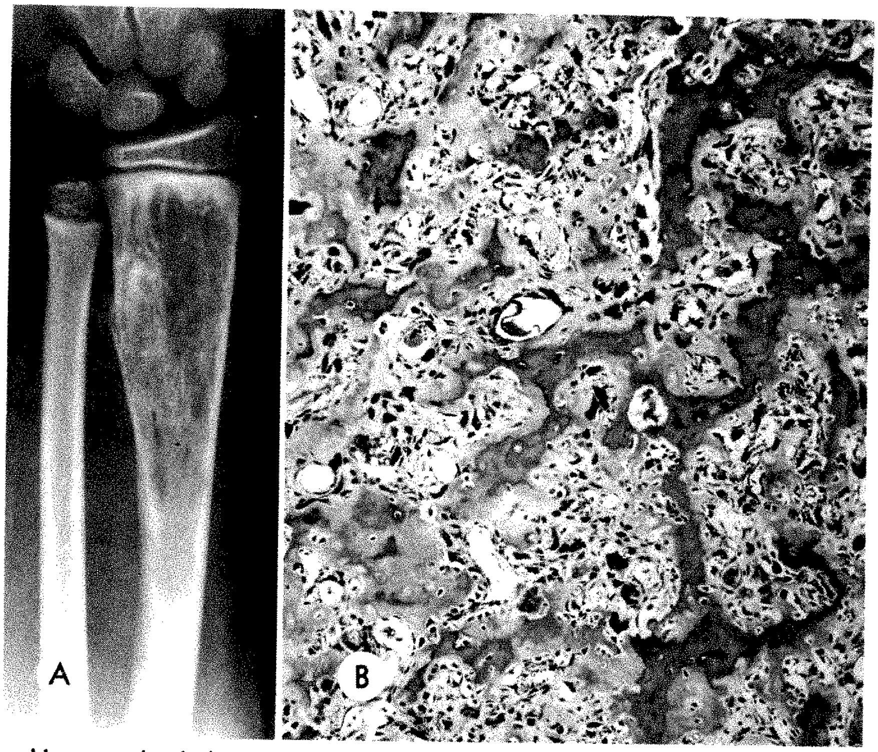

FIG. 10. Osteoblastoma simulating osteogenic sarcoma. (*A*) Large mineralized tumor in the distal radius of a nine year old boy. Initial impression was osteogenic sarcoma. Patient refused amputation, was treated with curettage, and is well without recurrence six years later. (*B*) Osteoblastoma with prominent irregularity of many component osteoblasts. The nuclei are large and bizarre in shape but mitoses notably infrequent. Misinterpretation as osteosarcoma is highly probable, although nuclear abnormalities may be "degenerative." (Hematoxylin and eosin; ×100.)

and ossified in 48 percent. Two tumors showed a centrally placed, densely ossified nidus (Fig. 13*A*). Expansion was common —present in 78 percent of the cases. Nine percent were judged to be mild, 43 percent moderate, and 26 percent markedly expanded (Fig. 13*D*). Definite cortical destruction was seen in 22 percent (Fig. 13*B*). The remainder exhibited an intact cortex. Scoliosis was observed in 30 percent and may be a helpful clue in detecting the more subtle tumors.

Retrospectively, we believed that benign osteoblastoma was the most likely diagnosis in 30 percent, either osteoblastoma or aneurysmal bone cyst in 26 percent, and either osteoblastoma or osteoid osteoma in 13 percent. Thus, when the tumor occurred in the spine, osteoblastoma could be suspected in about two-thirds of the cases.

TREATMENT AND PROGNOSIS

The follow-up in this series, which averaged approximately six and one-third years, establishes nearly always the benign course of this lesion and confirms its almost universally good response to conservative surgical treatment.

Cure can be expected after complete removal by either excision or thorough curettage. Incomplete removal will usually, although not always, result in recurrence. In our series, several cures resulted from subtotal excision. Moreover, two 14 year old patients with sacral tumors received no treatment after biopsy of the lesion. One of these was a 10 cm tumor that became densely ossified over the ensuing years; after 15 years this patient remains asymptomatic (Fig. 14). The other untreated lesion, a 4 cm sacral tumor, occurred in a

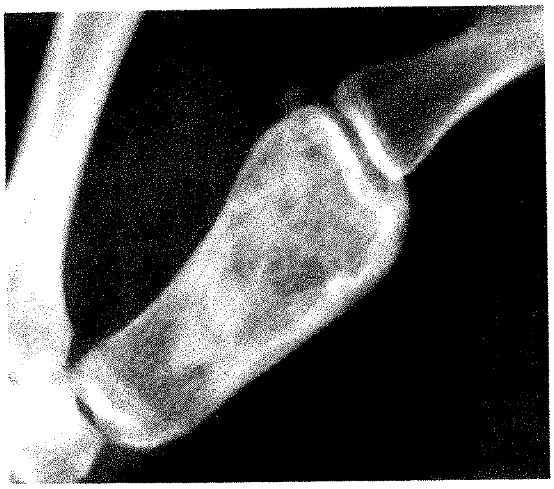

FIG. 11. Osteoblastoma of first metacarpal in a 25 year old man with expansile lesion with mineralized matrix and surrounding sclerosis.

boy who remains asymptomatic after seven years. Generally, however, the tumor grows slowly until removed. One woman had a tumor of the atlas documented roentgenographically in 1949; serial films showed gradual and relentless progression until she died in 1972 from local extension of the tumor. Similarly, two tumors of the vertebral column resulted in paraplegia.

One patient developed a Grade IV fibrosarcoma ten years after radiation therapy. Because of this potential hazard, radiation therapy should be avoided whenever possible.

SUMMARY

Benign osteoblastoma is a rare osteoblastic tumor of bone. The affected patients present usually with pain of long duration and often with a tender mass. Neurologic symptoms are common in vertebral lesions. There is a predilection for males and most of the patients are younger than 30 years of age. Favored sites include the spine, femur, tibia, and mandible.

The roentgenographic presentations are varied. The most diagnostic appearance in the long bones is one that resembles osteoid osteoma, but in which the nidus is too large (Fig. 12, *A–D*). Another fairly characteristic presentation is that of a ballooned tumor arising from the superficial aspect of the cortex of the diaphysis. Helpful signs include a mineralized matrix, marked reactive sclerosis, and abundant benign periosteal new bone formation. Unfortunately, only about a third of the appendicular lesions present in a diagnostic fashion. Perhaps the most important fact is that about one-fourth of the cases have roentgenograms consistent with malignant neoplasm (Fig. 12*F*). In the spine the tumor usually involves the dorsal elements. A benign-appearing, expansile tumor in the dorsal elements of the spine with a mineralized matrix is almost certainly an osteoblastoma. When the matrix is lucent, one cannot distinguish between osteoblastoma and aneurysmal bone cyst (Fig. 13*D*). As in long bone lesions, approximately one-fourth of these tumors have a roentgenographic appearance consistent with malignancy. Vertebral lesions may be extremely subtle and are easily missed by the unsuspecting radiologist or on films of poor quality.

Mandibular lesions usually have a typi-

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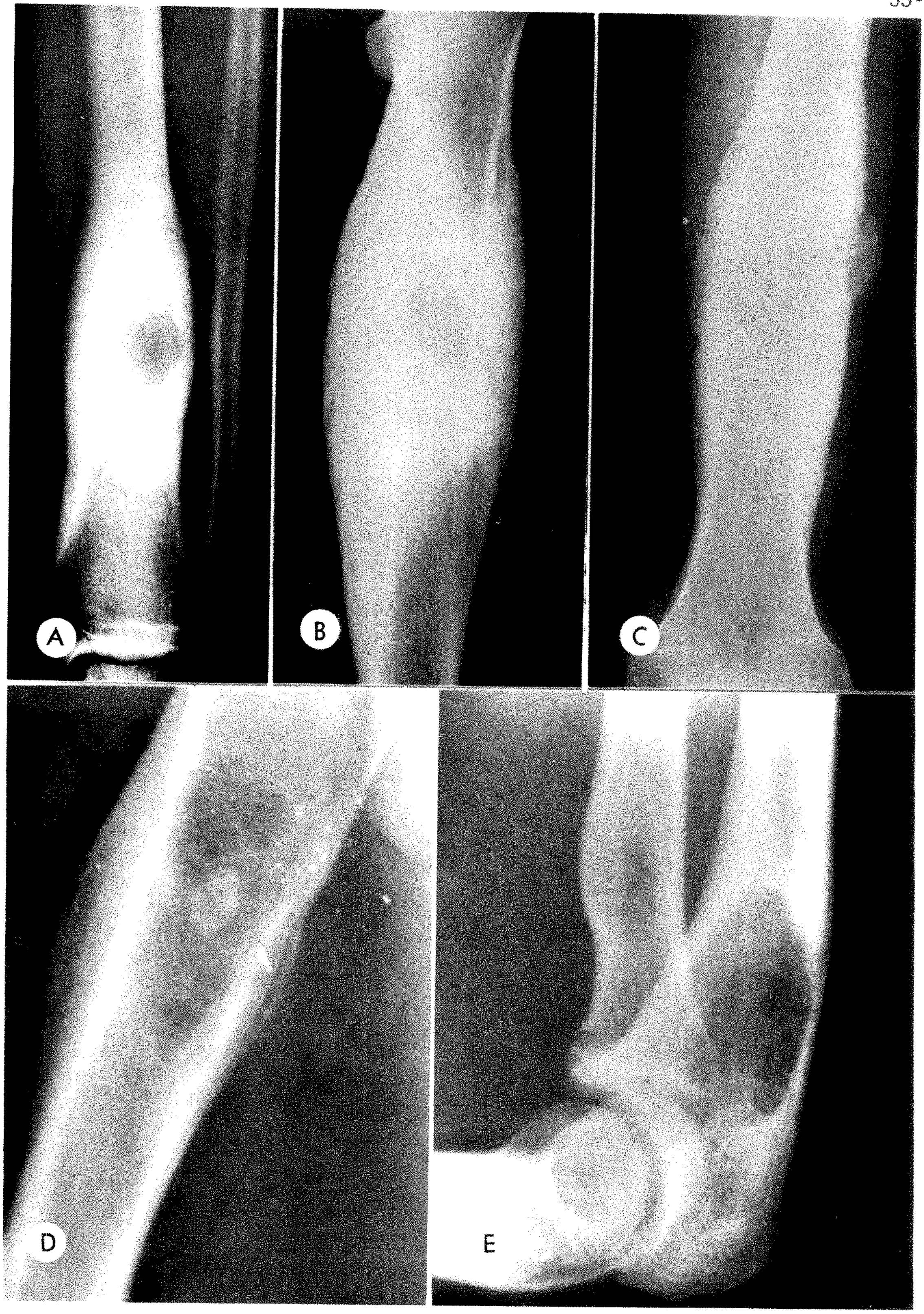
FIG. 12. Osteoblastomas of long bones. (*A*) Painful tumor (3 by 2 cm) in distal tibial diaphysis (note abundant surrounding sclerosis—more than 11 cm) of a 23 year old man who is well nine years after treatment. (*B*) Tumor (>2 cm) in proximal femoral diaphysis of a 14 year old boy with local pain relieved by aspirin. Note exuberant surrounding sclerosis and thick solid periosteal new bone. No recurrence 20 years after excision. (*C*) Lesion (3 cm) in femoral diaphysis of a 17 year old boy with limp and pain worse at night is obscured by abundant surrounding sclerosis and thick solid periosteal new bone. (*D*) Subtrochanteric lesion (4.5 cm) in a 14 year old boy with pain and limp for two months shows stippled ossification, laminated new bone, and a densely ossified nidus. Patient is well seven years after surgery. (*E*) Ulnar tumor (3.2 cm) was an incidental finding in a twelve year old girl. It is lucent and has a well-defined margin compatible with benign lesion. Specific diagnosis, however, is not possible.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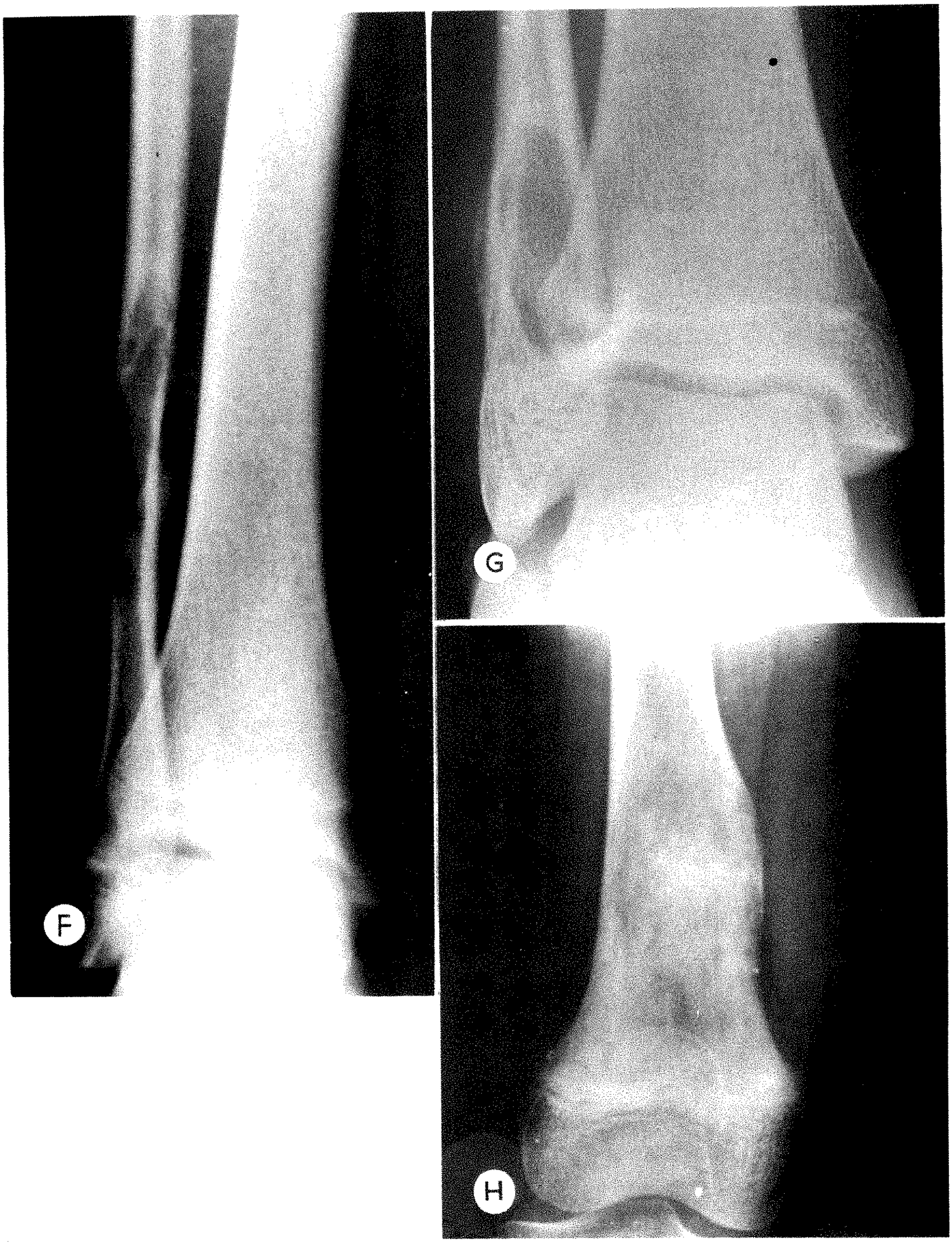

FIG. 12. (*F*) Poorly marginated fibular tumor with cortical destruction and Codman's triangle in a 14 year old boy. The impression from roentgenogram was Ewing's sarcoma. Patient is well eleven years after resection. Recurrence necessitated re-excision eight months after original surgery. (*G*) Lucent, well-marginated tumor in distal fibula of a 19 year old man. Note solid periosteal new bone. (*H*) Ossified tumor (5 by 3 cm) in distal femoral diaphysis of an eight year old girl. Despite mild expansion, the lesion was poorly marginated and caused concern over possibility of osteogenic sarcoma.

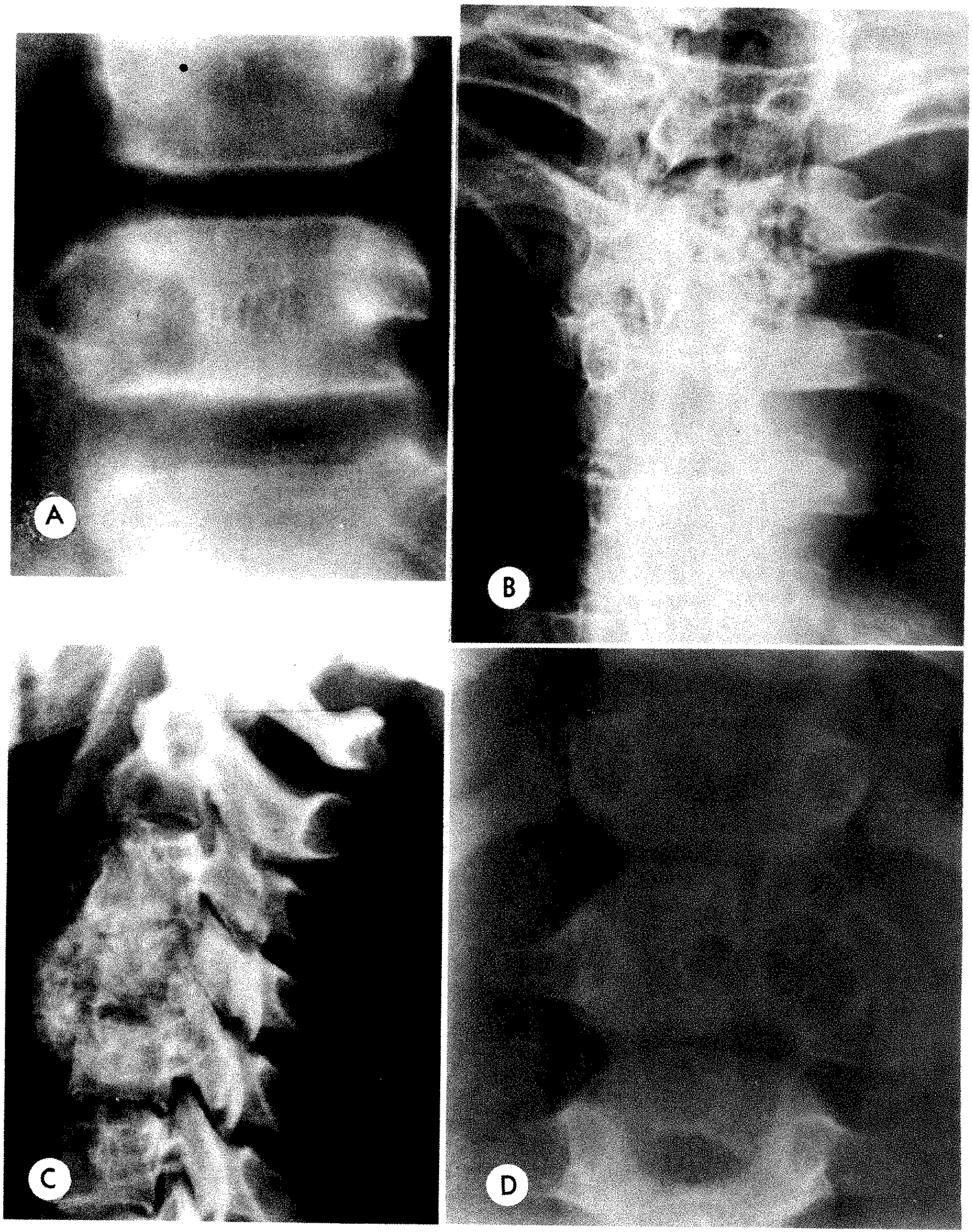

FIG. 13. Osteoblastomas of spine. (*A*) Expanding 3 cm tumor in L-4, lucent except for an ossified nidus, in a 14 year old boy. (*B*) Heavily mineralized tumor involving both body and dorsal elements of T-3 in a 20 year old man who had an 18 month history of pain followed by neurologic symptoms in both legs and is now well 14 years after subtotal excision and radiation. (*C*) Heavily mineralized tumor (5 cm) of C-4 in a 15 year old girl who had pain for 18 months and is now without recurrence two years after excision. (*D*) Lucent tumor (4 cm) of L-1 with significant expansion in a seven year old girl with a two month history of pain and fever. The presentation is compatible with either osteoblastoma or aneurysmal bone cyst.

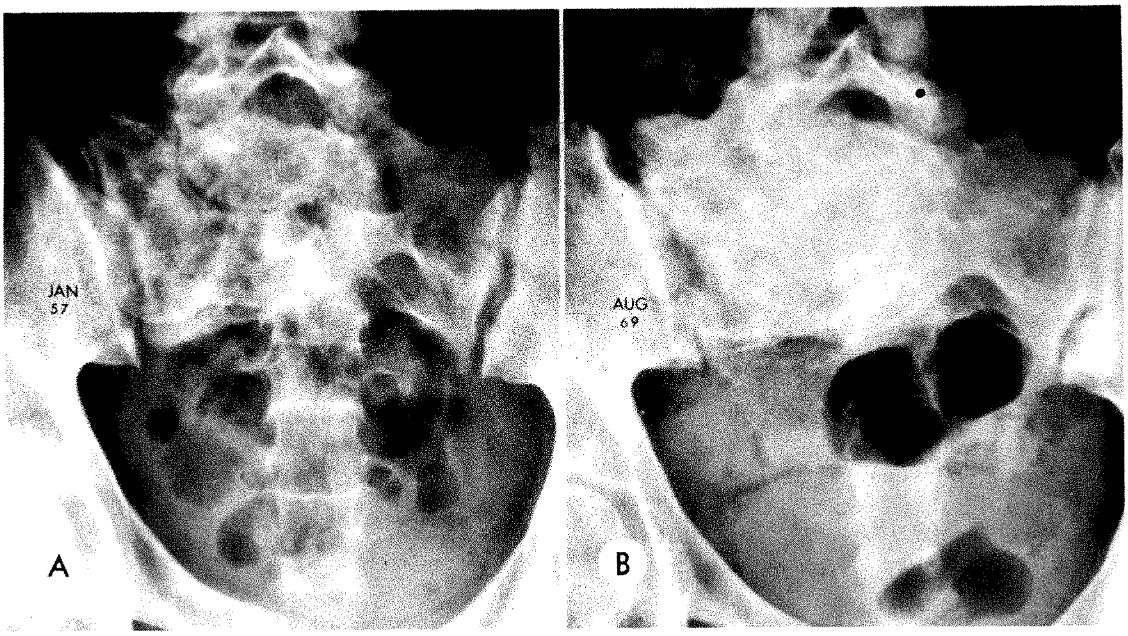

FIG. 14. Untreated osteoblastoma. (*A*) Large sacral tumor (10 cm) in a 14 year old girl. (*B*) A roentgenogram twelve years later shows increased ossification but no growth despite lack of therapy.

cal appearance consisting of a spherical ossified tumor surrounded by a well-defined radiolucent halo. They are usually adjacent to or engulfing a tooth root (Fig. 6).

The close relationship of osteoid osteoma and osteoblastoma cannot be ignored. Because of the difference in the clinical course, it is worthwhile to separate the two. Cytologic pattern, size, roentgenographic appearance, and pain pattern will distinguish most cases. When lesions are borderline, we use a diameter of 1.5 cm as an arbitrary means of separating the two.

Perhaps the most important aspect of osteoblastoma is its distinction from osteogenic sarcoma. Adequate biopsy material is imperative. We have seen three cases in which low grade osteogenic sarcoma was so well differentiated that an erroneous diagnosis of osteoblastoma was made. Fortunately, this is a rare occurrence and this mistake will decrease as the experience of the pathologist increases. We believe that today, with our greater experience, none of these cases would be called osteoblastoma. There was one case in this series (Fig. 9), however, in which the original tissue even in retrospect is compatible with osteoblastoma, although tissue obtained nearly four years later is obviously osteogenic sarcoma. The roentgenograms changed similarly over this four year period. This case may represent osteogenic sarcoma with areas simulating osteoblastoma rather than malignant transformation. In another case in this series, both benign and malignant areas coexisted in a lesion of long duration; subsequently, metastases developed.

Three cases in this series were osteoblastomas in which the osteoblasts were large, varied in size and shape, and contained bizarre nuclei, which led to one erroneous diagnosis of osteogenic sarcoma. This patient, a nine year old boy with a 7.7 cm lesion in the distal radius, fortunately refused amputation and was therefore treated by simple curettage. He is well without recurrence six years later (Fig. 10*A*).

The roentgenographic findings should always be considered even though they may be misleading. We have seen several cases in which the roentgenogram was compatible with benign osteoblastoma and yet the histology was highly malignant. Three of these cases were multifocal, containing multiple small tumor masses within sclerotic nontumorous bone (Fig. 8).

Conservative surgery is the treatment of choice.

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NON-RHEUMATIC ACUTE MITRAL INSUFFICIENCY CAUSED BY RUPTURED CHORDAE TENDINEAE*

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ABSTRACT:

Five patients with proved mitral insufficiency caused by ruptured chordae tendineae were examined. Two patients came to autopsy without cardiac cateterization. Three patients, who had cardiac cateterization and surgical replacement of their mitral valves, improved dramatically. Two additional patients have been clinically diagnosed and have had corroborative cardiac catheterization and are being observed in anticipation of possible future valve replacement.

Similar findings in these seven patients include adult onset of a characteristic systolic heart murmur which mimics aortic valvular stenosis, acute pulmonary edema associated with massive mitral insufficiency in the face of a normal sized or only minimally enlarged left atrium, and variable size of the left ventricle. In none of the patients were there historical or physical findings of trauma or rheumatic or bacterial endocarditis.

A wide spectrum of clinical courses may be explained by the variable number of ruptured chordae tendineae at the time of clinical presentation. Although the incidence and etiology are uncertain, we believe this entity is not uncommon. Myxomatous degeneration of the connective tissue of the heart was present, but the cause remains unknown.

RUPTURE of chordae tendineae leading to mitral insufficiency has been known for over a century. Despite recent reports of small series of patients with mitral incompetence due to ruptured chordae tendineae, its etiology and incidence have remained poorly understood. The increasing number of reported cases would indicate an enhanced awareness of this disorder.[2,5,6,9] Evaluation of seven patients with mitral insufficiency secondary to rupture of chordae tendineae, cared for by a single cardiologist over a brief period of time, leads us to believe that it probably is a common entity.

Correlation of the clinical, roentgenographic, anatomic and histologic findings in the seven patients in this study revealed common features to substantiate, in agreement with others, that mitral insufficiency secondary to ruptured chordae tendineae is a clinically identifiable entity, which may on occasion require immediate surgical attention.[1,7] The purpose of this report is to further increase the index of suspicion of this syndrome.

MATERIAL

Seven patients who had pulmonary edema associated with acute mitral insufficiency were examined. They were divided into three groups based on their clinical courses.

Group I represents the first two patients who had a clinical diagnosis of mitral insufficiency secondary to ruptured chordae tendineae. These two individuals died without cardiac catheterization or benefit of surgery and were autopsied.

Group II represents three patients who

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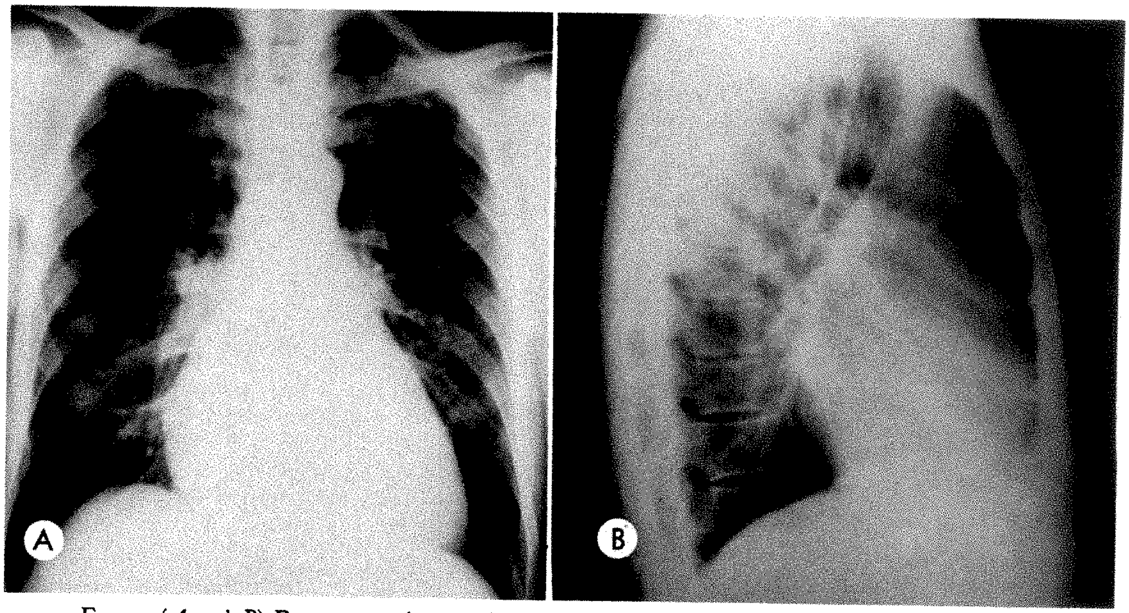

FIG. 1. (*A* and *B*) Posteroanterior and lateral chest roentgenograms of patient 1 at time of clinical diagnosis of ruptured chordae tendineae. No significant cardiomegaly is identified.

had confirmatory cardiac catheterization and subsequent mitral valve replacement with Starr-Edwards prostheses. The resected mitral valve leaflets and chordae tendineae were studied grossly and histologically.

Group III represents two patients in whom the clinical diagnosis was supported by cardiac catheterization and angiography. Although these patients were acutely ill, they are now medically stable and are being observed in consideration for surgery.

GROUP I

Patient 1. This white male had annual employment physical examinations, and a systolic murmur was first detected at age 60 years. He was asymptomatic and remained so until age 66 when he experienced sudden onset of congestive heart failure. Significant physical findings included a pansystolic murmur radiating to the sternum, but with poor radiation into the axilla. Chest roentgenograms demonstrated minimal left ventricular elongation with a normal cardiothoracic ratio (Fig. 1, *A* and *B*). His electrocardiogram was interpreted as showing atrial fibrillation, left ventricular hypertrophy by voltage criteria, and right bundle branch block. After appropriate therapy, he became comfortable.

In the next four years prior to death at age 70, he had multiple admissions for recurrent and advancing congestive heart failure. The terminal admission was for severe congestive heart failure associated with pulmonary infarction. Although mitral insufficiency with suspicion of ruptured chordae tendineae was correctly diagnosed, cardiac catheterization with surgical intent was not performed because of his age. At necropsy, the chordae tendineae were ruptured at their insertion into both the anterior and posterior mitral leaflets (Fig. 2).

Patient 2. This 61 year old white male was well and able to work two weeks prior to acute onset of severe congestive heart failure. He was known to have a heart murmur for several years. On examination, a holosystolic murmur with ejection characteristics was noted radiating from the cardiac apex to the cardiac base but not into the axilla. Chest roentgenograms revealed severe pulmonary edema with normal heart size (Fig. 3). An electrocardiogram was essentially normal with normal sinus rhythm. Diagnosis of acute mitral insufficiency secondary to rupture of chordae tendineae was strongly considered but he expired prior to planned cardiac catheterization. At autopsy, multiple ruptured chordae tendineae were demonstrated with myxomatous degeneration of the mitral valve leaflets ("floppy mitral valve")

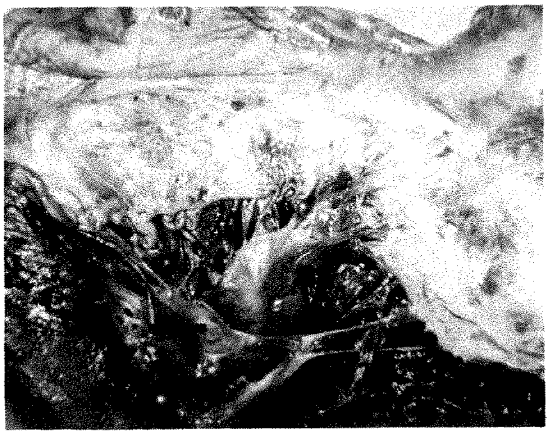

Fig. 2. Autopsy specimen of the same patient as in Figure 1. Numerous ruptured chordae tendineae are evident.

(Fig. 4; and 5). These findings were reviewed and confirmed by Dr. William C. Roberts, Chief, Section of Pathology of the National Heart and Lung Institute.

Comment. In the two patients in this group, a characteristic heart murmur was known for years, but symptoms of congestive heart failure leading to death lasted for four years in Patient 1 and only two weeks in Patient 2. Chest roentgenograms and electrocardiograms were consistent with only minimal cardiac enlargement, and there was no significant left atrial abnormality seen on electrocardiography or chest roentgenography.

GROUP II

The three patients who had cardiac catheterization and valve replacement were males, and their respective ages at the time of catheterization was 61, 53, and 56 years. Each had the characteristic systolic apical murmur that radiated to the base of the heart and not into the axilla. The heart murmurs were known to exist from five to nine years prior to the clinical diagnosis of ruptured chordae tendineae. In one patient, aortic stenosis was suspected clinically because of the ejection quality of the heart murmur and its radiation characteristics.

Intermittent symptoms of congestive heart failure lasted for ten years, one year and six months prior to cardiac catheterization and subsequent surgery in the three patients of this group. Each of the three patients had regular sinus rhythm initially and the electrocardiographic voltage was within normal limits. Except for one example of striking left axis deviation, the electrocardiograms were interpreted as normal. Moderate to severe left ventricular enlargement was recorded on roentgenography but in none of these patients was there evidence of more than minimal left atrial enlargement (Fig. 6*A*).

Results of cardiac catheterization were strikingly similar in the three patients. Each was noted to have pulmonary hypertension (80, 90 and 100 mm Hg peak systolic pressure). The pulmonary artery wedge pressure indicated marked mitral regurgitation (V wave measured 58 to 60 mm Hg). Cine ventriculography was performed in each patient in the right anterior oblique projection and identical findings of massive mitral insufficiency were demonstrated (Fig. 7).

Surgical replacement of the mitral valve in each of these patients was followed by dramatic relief of symptoms. On follow-up chest roentgenograms, the heart size became normal (Fig. 6*B*). Symptoms of heart failure have not recurred since surgery; the period of follow-up is eight months to two years.

Histologic examination of the resected valves and chordae tendineae revealed similar findings. In none could Aschoff's bodies be detected. The

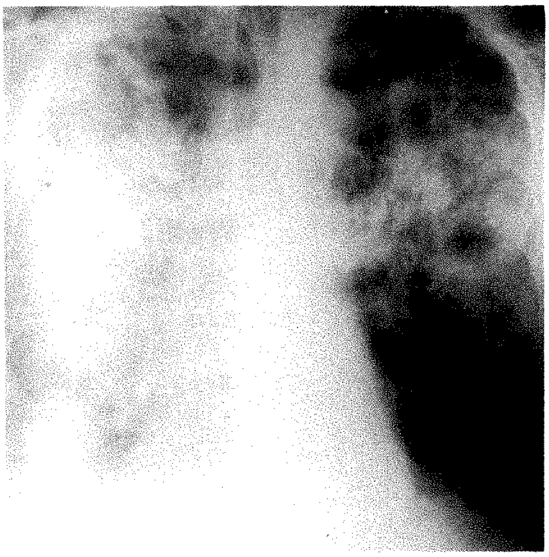

Fig. 3. Second patient who expired with mitral insufficiency from ruptured chordae. Admission chest roentgenogram reveals severe pulmonary edema with normal heart size.

valves were not grossly thickened but areas of myxomatous degeneration and fibrocartilaginous thickening were seen on microscopic sections of the valve leaflets and the chordae tendineae (Fig. 8, *A* and *B*).

In two of these patients, the chordae tendineae to the posterior leaflet alone were ruptured. In the remaining patient, multiple chordae tendineae to the anterior and posterior leaflets were detached.

Comment. Similarities and differences are apparent in this group as compared to the first group. Similar types of systolic murmurs with nonradiation to the axilla were present in the patients of Groups I and II. Although pulmonary edema was present clinically and roentgenographically, the heart was not enlarged in the patients of Group I, whereas each of the three patients who had successful surgery for repair of mitral incompetence had moderate cardiomegaly. None of the patients in either group had more than minimal left atrial enlargement despite marked mitral insufficiency. In general, if health permits, age is no longer considered a reason not to submit a patient to cardiac catheterization or surgery.

GROUP III

The two remaining patients have followed a course identical to that seen in Group II. They are both males, ages 70 and 67. Each experienced the acute onset of pulmonary edema and had "asymptomatic" systolic heart murmurs known for several years. No other significant past history was recorded.

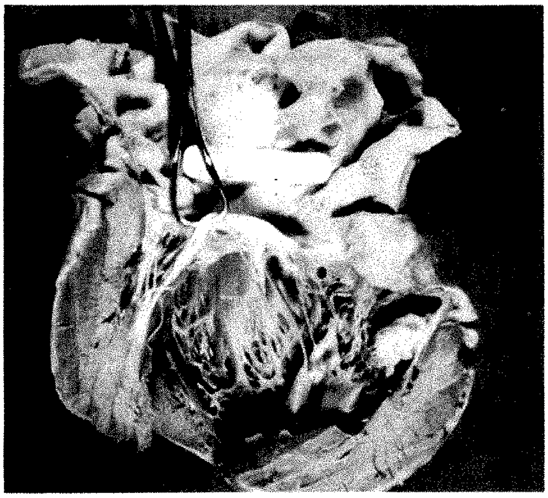

Fig. 4. Autopsy specimen of same patient as in Figure 3 with multiple ruptured chordae tendineae.

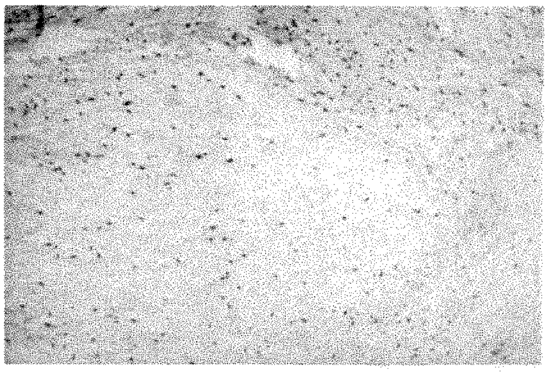

Fig. 5. Histologic sections of mitral valve of heart in Figure 4. Myxomatous replacement of normal architecture is present.

On physical examination, an apical holosystolic murmur was heard in each of the two patients, radiating to the sternum. Chest roentgenograms showed only minimal left ventricular and left atrial enlargement (Fig. 9, *A* and *B*). The electrocardiogram was normal in one patient and borderline left ventricular hypertrophy was noted in the other. Initially, both patients had a regular sinus rhythm.

Cardiac catheterization was performed in each of the two patients in this group and revealed different results. The first patient, symptomatic with dyspnea, had a mean pulmonary capillary wedge pressure of 30 mm Hg with a peak V wave of 45 mm Hg. The other patient, who achieved an asymptomatic state on full therapy, had only slight elevation in pulmonary artery pressures (mean pulmonary artery wedge pressure—10 mm Hg, peak pressure (V wave) 12 mm Hg). Cine ventriculography in each of the patients revealed similar findings of gross mitral insufficiency (Fig. 10). Both patients in this group responded well to therapy, and heart size returned to normal on roentgenography. In the year following cardiac catheterization, pulmonary edema has not recurred.

DISCUSSION

The study of seven patients in this series demonstrates sufficiently similar findings

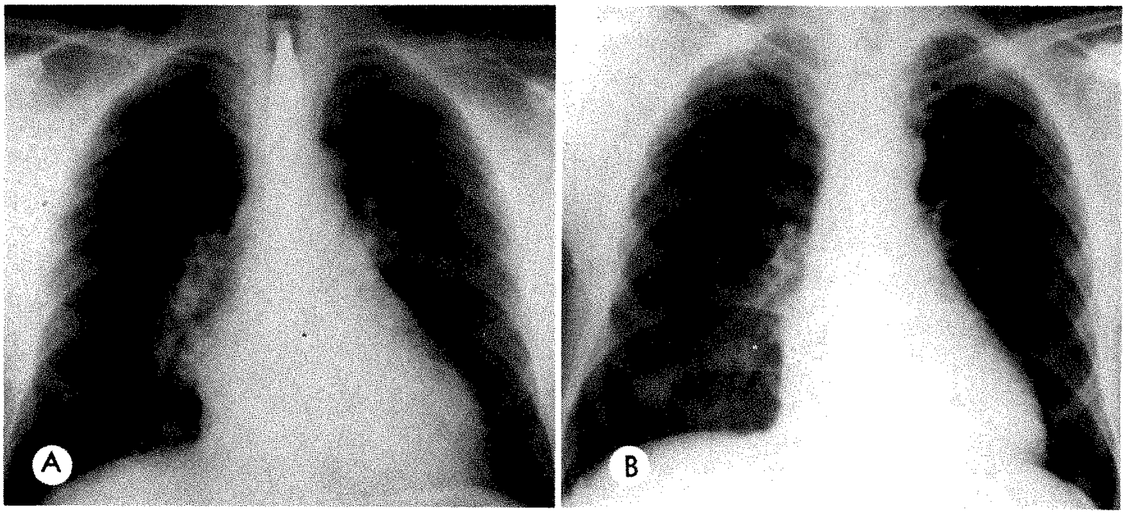

Fig. 6. (*A*) Cardiomegaly from ruptured chordae prior to surgery. (*B*) After surgical replacement of mitral valve, heart size has returned to normal.

to provide a well defined syndrome. All were males, their ages ranged from 53 to 70 years at the time of definitive diagnosis. None had a history of myocardial infarction, angina pectoris, rheumatic fever or bacterial endocarditis, systemic hypertension or trauma. Blood cultures were negative in all patients.

Each patient developed a characteristic holosystolic apical murmur during mid or late adulthood. The unusual radiation toward the sternum without radiation to the axilla mimicked aortic stenosis in two patients. This has been a common experience and there are reports of single cases emphasizing this similarity.[4,8] Explanation of this unusual murmur is the selective rupture of chordae tendineae to the posterior leaflet. The posterior chordae tendineae are thinner and more susceptible to rupture. The resultant regurgitant jet strikes the interatrial septum adjacent to the aortic root and transmits the murmur to the basilar portion of the heart. This characteristic murmur is the most specific single clinical finding of the syndrome.

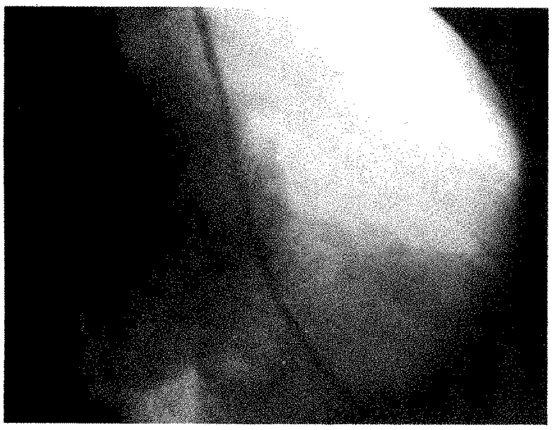

Fig. 7. Selected frame from cine left ventriculogram in ventricular systole demonstrates massive mitral insufficiency. The posterior leaflet is seen to evert into left atrium.

Idiopathic hypertrophic sub-aortic stenosis (IHSS) may mimic the syndrome of mitral insufficiency secondary to ruptured chordae tendineae. IHSS is frequently associated with mitral insufficiency and a basilar systolic murmur which mimics valvular aortic stenosis. The heart size and configuration on chest roentgenograms are similar in the two entities. The most significant differentiating feature is that arterial pulsations are usually brisk in both but of bisferious quality in sub-aortic stenosis.

With excellent cine roentgenograms, mitral insufficiency caused by ruptured chordae tendineae may be diagnosed with accuracy; hence ventriculography and assessment of pulmonary artery and pulmonary capillary wedge pressures should be a standard part of the examination in patients suspected of having ruptured chordae tendineae.[8]

In this series of patients, symptoms could not be correlated with known duration of murmur, electrocardiographic findings or chest roentgenographic findings. Nevertheless, a small heart on roentgenography with pulmonary edema was more likely to have a less favorable response to medical therapy (patients in Group I) than cardiomegaly and mitral insufficiency which responded well to surgery (Group II).

Despite massive mitral insufficiency demonstrated on cine ventriculography, the left atrium was either normal or only minimally enlarged on roentgenography and was recorded as normal on electrocardiography in five of the seven patients who had regular sinus rhythm. Electrocardiograms of the remaining two patients with atrial fibrillation do not allow evaluation of the atrial electrophysiology. It is well accepted that the normal left atrium, suddenly exposed to mitral regurgitation, is not compliant and does not expand; thus, the full brunt of the peak left ventricular systolic pressure is transmitted directly to the pulmonary vascular bed.

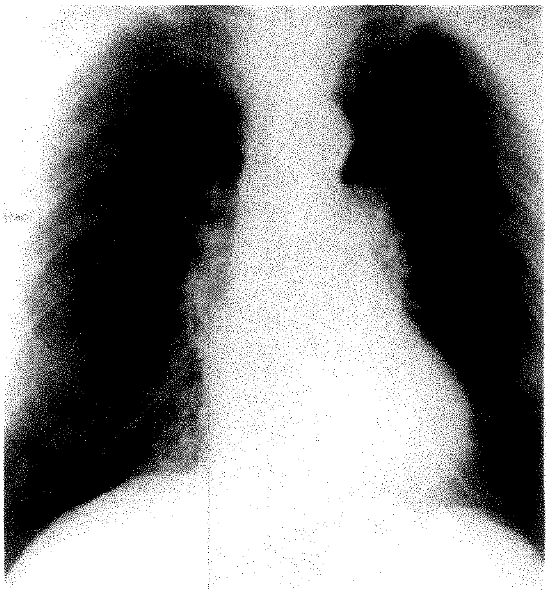

Fig. 9. Clinically diagnosed ruptured chordae tendineae with only minimal cardiomegaly and no apparent left atrial enlargement.

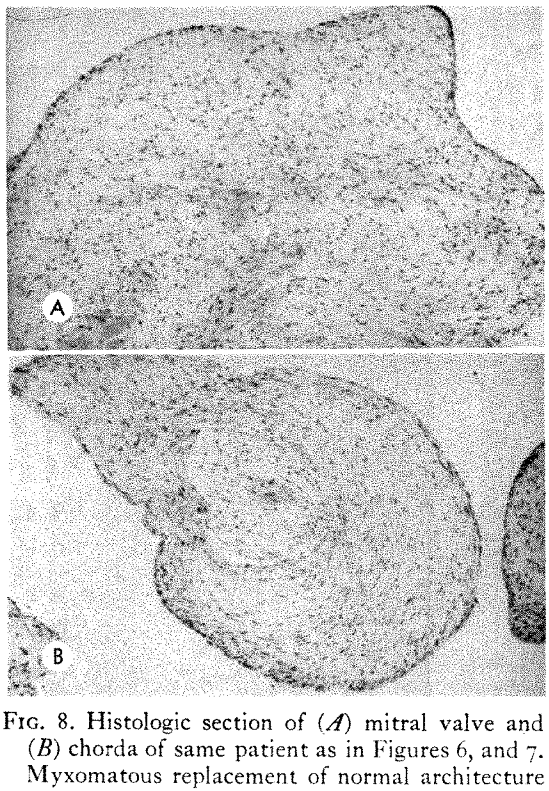

Fig. 8. Histologic section of (*A*) mitral valve and (*B*) chorda of same patient as in Figures 6, and 7. Myxomatous replacement of normal architecture is seen in valve leaflet in (*A*) and in the chorda in (*B*).

There is probably a wide spectrum of clinical states depending upon the severity of mitral insufficiency and the number of ruptured chordae tendineae. Thus, abrupt, unrelenting heart failure with sudden death may occur in a matter of weeks (Patient 2) or slowly progress over a period of years (Patient 1, 3; and 5). In each of the patients in Groups I and II, definitive surgery appeared indicated, however, it is possible that an arrested state may exist where surgery may not be necessary, as in the patients of Group III.

There are approximately 120 chordae tendineae extending from the two papillary muscles of the left ventricle to the anterior and posterior mitral leaflets. Rupture of a few chordae tendineae may produce the characteristic heart murmur but not significant mitral insufficiency with pulmo-

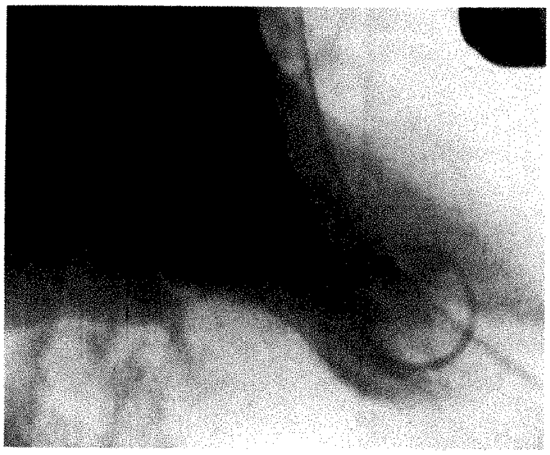

FIG. 10. Cine left ventriculogram (systolic phase) of same patient as in Figure 9. Massive mitral insufficiency with eversion of posterior mitral leaflet into atrium is evident.

nary edema. It is unknown what number of ruptured chordae tendineae is required to cause pulmonary edema.

Although the etiology of spontaneous rupture of chordae tendineae is uncertain, rheumatic and bacterial endocarditis, arteriosclerosis, and congenital anomalies have been excluded in this and other series. The clear finding of myxomatous degeneration in the valves and chordae would suggest a form of connective tissue degeneration.[3] In Patient 2 mucoid degeneration of the mitral valve leaflet, as seen in "floppy valve syndrome" was also diagnosed. No other features to suggest Marfan's syndrome or Ehlers-Danlos syndrome were present in any of the patients in this report. Late onset of findings in adult life would also argue against these connective tissue disorders as a significant contributing factor unless a *forme fruste* of this syndrome is present.

The clinician, fully aware of this syndrome of spontaneous ruptured chordae tendineae, is in a position to prevent unnecessary fatality since mitral valve replacement has been totally curative in the three patients in Group II. Awareness that massive mitral insufficiency secondary to ruptured chordae tendineae may occur in a patient with normal left ventricular and atrial size will alert one to a more careful assessment of physical findings and history. The authors suspect that this syndrome is relatively frequent and that misdiagnosis or lack of full penetrance until later adult years are the reasons for its apparent rarity.

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VOL. 126, NO. 2

HEMOCHROMATOSIS: A DISEASE OFTEN SILENT BUT NOT INVISIBLE*

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ABSTRACT:

Hemochromatosis is a disorder characterized by the association of portal cirrhosis with deposition of excess amounts of iron in the parenchymal cells of many organs. Arthralgia and arthritis occur in about 50 percent of patients. The role of the radiologist is often significant in the recognition of this condition because hemochromatosis may be unsuspected clinically since the hepatic cirrhosis is frequently inactive at the time the arthritis develops. The possibility of hemochromatosis should be considered when the characteristic involvement of the metacarpophalangeal, radiocarpal, and proximal interphalangeal joints of the hand and wrist is present. In addition, articular and fibrocartilage calcification is often noted, particularly in the knee, triangular cartilage of the wrist, hip, elbow, symphysis pubis, and shoulder. Although localized chondrocalcinosis may be seen in association with many disorders, as well as in asymptomatic elderly persons, generalized chondrocalcinosis is a significant finding and is commonly associated with hemochromatosis. Recognition of the typical distribution of the arthropathy plus its characteristic roentgenographic features should aid in the identification of patients with the disorder who do not demonstrate the typical clinical features of hemochromatosis.

HEMOCHROMATOSIS is a disorder characterized by the association of portal cirrhosis with deposition of excessive amounts of iron in the parenchymal cells of many organs of the body including the liver, pancreas, spleen, gastrointestinal tract, kidneys, heart, and endocrine glands. It may be idiopathic or secondary to other conditions including sideroblastic anemias, myelofibrosis, portocaval shunt procedures, the exogenous administration of iron as with transfusion therapy for chronic anemias, and porphyria cutanea tarda.[10]

INCIDENCE

Idiopathic hemochromatosis is said to occur in one of 800 to one of 7,000 hospital deaths.[11,20] The majority of patients do not develop symptoms until 40 years of age or more. Men are affected ten times as often as women, probably due to the increased incidence of cirrhosis in men and the natural iron loss in women during menstruation, pregnancy, and lactation.[11,20,34]

PATHOGENESIS

Under physiologic conditions iron enters the body by way of the gastrointestinal tract. The amount of dietary iron is quite variable. It depends upon the amount of meat eaten, the type of vegetables and beverages ingested, and the type of cooking utensils used. The average American diet contains between 5 and 15 mg of iron daily of which approximately 1 mg is absorbed by a normal adult man and slightly more by women and children.[24]

The factors responsible for regulating iron absorption have not been fully elucidated. The greater the amount ingested, the more absorbed, irrespective of bodily needs.[2] The iron initially enters the intestinal epithelial cells where a portion remains in the form of ferritin. If the iron is not transported from the cells into the plasma, it will be "re-excreted" into the intestinal lumen with the natural desquamation of the epithelial cells. In the normal person, about 50 percent of the iron in the mucosal cells will be absorbed and the rest returned to the lumen with the sloughed cells, whereas, only five percent of the iron will be subsequently eliminated with the mucosal cells in the presence of iron deficiency.[3] The amount of iron present in the mucosal cell itself may be a factor regulating plasma absorption of iron.[8] Other factors affecting the rate of absorption include the presence of chronic liver disease,[7,12] poorly defined components of gastric juice,[27] dietary factors such as phytates and phosphates which bind iron,[17,33] and reducing substances which convert ferric to ferrous iron.[23] The level of erythropoietin may also influence absorption.[22]

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Iron passing into the blood stream is bound to a specific transport protein, transferrin. Within 60 to 120 minutes it leaves the plasma and goes mainly to the bone marrow and liver where it is stored in the reticuloendothelial cells in the form of ferritin and hemosiderin.[4] In states of iron overload, increased amounts of hemosiderin can be demonstrated in many organs of the body. In the absence of cellular damage and fibrosis, this condition is called hemosiderosis. If cellular injury and fibrosis are also present, the condition is called hemochromatosis.

A unique characteristic of iron metabolism is the fact that once the iron has been absorbed, it is conserved and recycled such that only minimal quantities of iron are excreted.[15] Relatively minute quantities are lost in sweat, hair, feces, and urine. The only significant loss of iron is by menstruation, pregnancy, lactation, and bleeding.

From this description of normal iron metabolism it becomes apparent that increased iron storage may be the result of increased intestinal absorption from a diet containing a normal amount of iron; it may be due to a significant increase in the amount of iron ingested; or it may occur due to the exogenous administration of parenteral iron (secondary hemochromatosis).

The etiology of idiopathic hemochromatosis is unknown. There is considerable debate as to whether it represents an inborn error of metabolism, characterized by the increased absorption of iron from the gastrointestinal tract in the presence of a normal dietary intake of iron, or if it is due to excess iron in the diet. A second controversy revolves around whether the massive accumulation of iron is responsible for the cellular injury and fibrosis, or conversely, whether hemosiderin deposits have no harmful effect and do not inevitably lead to cellular damage and hemochromatosis.

Many patients with idiopathic hemochromatosis have histories of chronic alcohol abuse and malnutrition.[11,29,34] Wine commonly contains 15 to 20 mg, sometimes up to 50 mg, of iron per liter.[25] This probably accounts for some of the cases of hemochromatosis. Familial aggregations have been described among persons without histories of alcohol or iron excess, supporting the concept that in some people the

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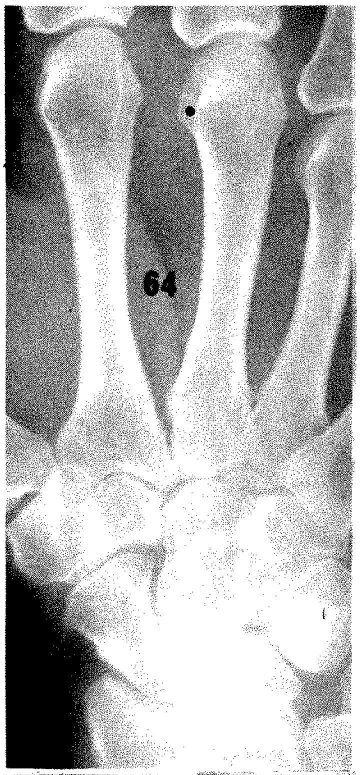
FIG. 1. Progressive changes of the right second and third metacarpophalangeal joints and wrist in a patient with hemochromatosis: 1964, normal study; 1966, mild narrowing of the second and third metacarpophalangeal joints; 1967, further metacarpophalangeal joint narrowing plus sclerosis and cyst formation in the metacarpal heads as well as early radial rotation of the scaphoid; 1969, further metacarpophalangeal joint narrowing and sclerosis plus development of hypertrophic bone resulting in actual bony enlargement of the metacarpal heads, and early narrowing of the joint between the scaphoid and trapezium; 1974, further bony enlargement and joint narrowing of the second and third metacarpophalangeal joints, with the fourth and fifth joints unaffected, and nonuniform carpal joint narrowing between the scaphoid and trapezium and between the lunate and capitate. Faint triangular cartilage calcification is present.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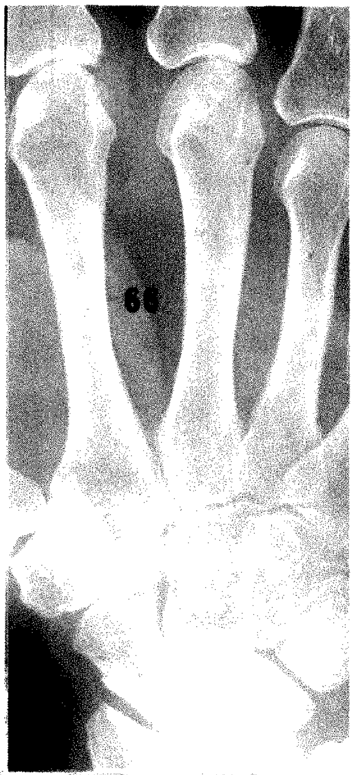
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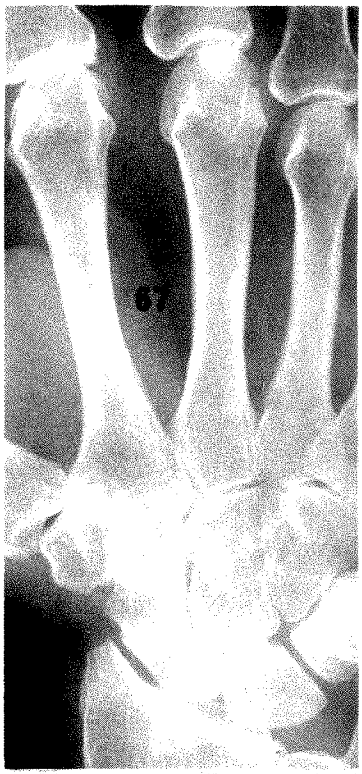
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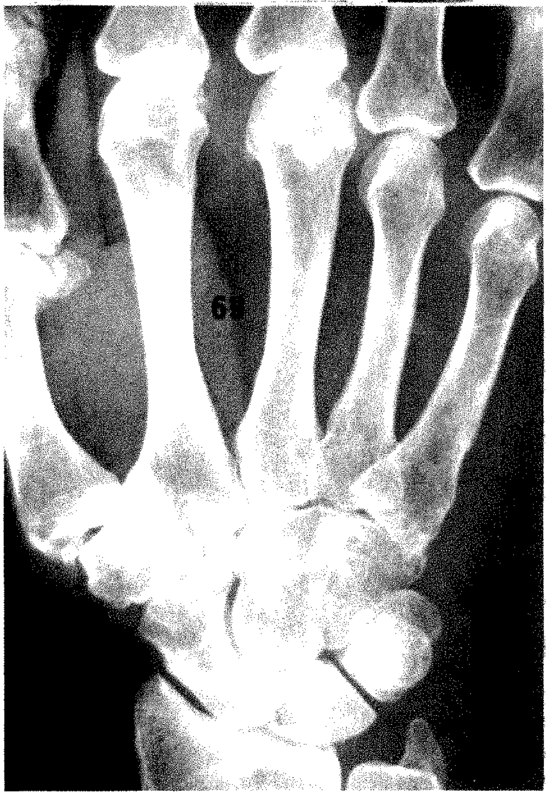
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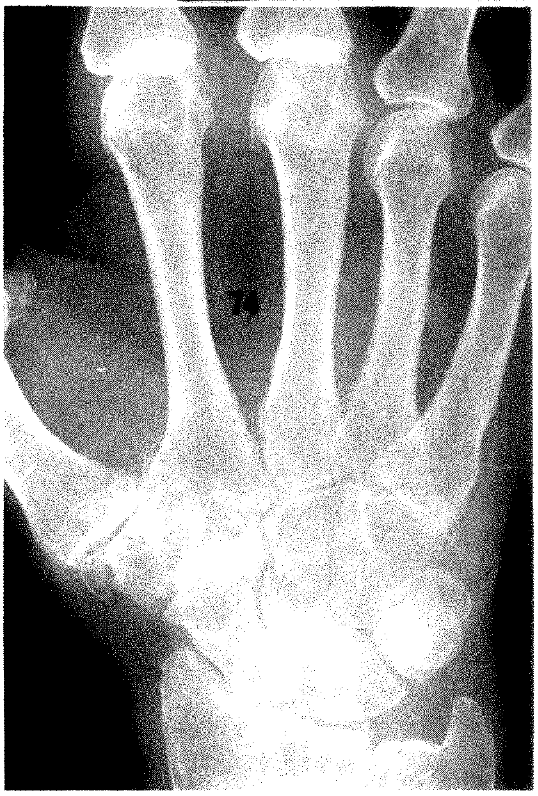
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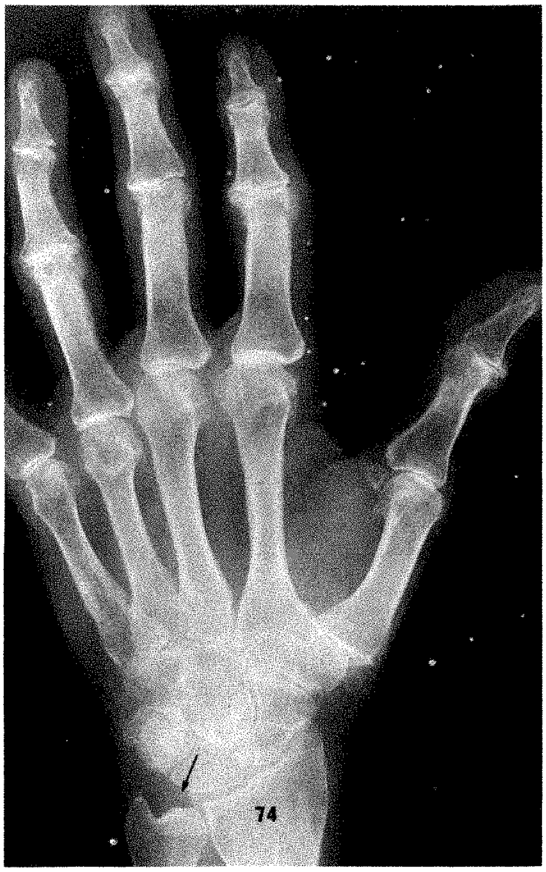

Fig. 2. The left hand of the same patient in Figure 1. In addition to the metacarpophalangeal joint narrowing, bony enlargement of the metacarpal heads, nonuniform carpal joint narrowing and cartilage calcification (arrow), there are joint narrowing and hypertrophic osteophyte formation involving the proximal and distal interphalangeal joints. The proximal and distal interphalangeal joints of the right hand are similarly affected.

condition may result from an inherited metabolic defect.[5,11,28] Idiopathic hemochromatosis is undoubtedly a disorder caused by various etiologies and is, therefore, a syndrome and not a disease.

CLINICAL FEATURES

The clinical features are variable with the symptoms in about one-half of the patients referable to liver disease including hepatomas, and the initial complaints in the remainder due to pneumonia, other infections, cardiac decompensation, diabetes mellitus, and cerebrovascular accidents.[20] The hepatic cirrhosis is often inactive at the time of diagnosis of the disease, therefore, jaundice and hepatic failure are not prominent features.[11,20,34] Arthralgia and arthritis occur in about 50 percent of patients.[9,16,32] The arthritis frequently begins in the metacarpophalangeal joints. Although it may be confined to the hands and wrists, it usually progressively involves larger joints. About one-third of patients experience arthritis prior to or concurrent with the first symptoms of hemochromatosis, whereas the re-

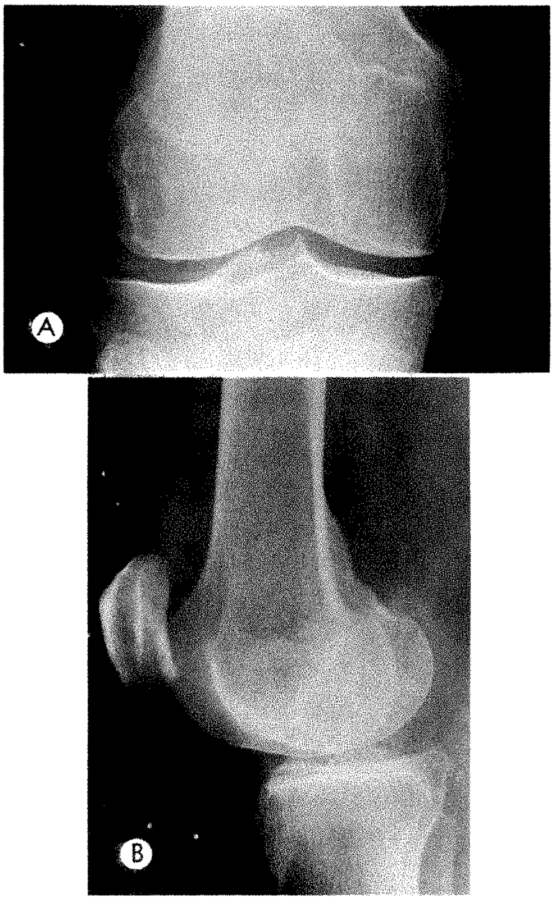

Fig. 3. (*A*) Frontal projection of the knee demonstrates calcification of the menisci without significant joint narrowing or hypertrophic osteophyte formation. (*B*) Lateral view demonstrates calcification in the suprapatellar and infrapatellar tendons. Very faint articular cartilage calcification is present along the femoral condyle posteriorly. Joint effusion is present.

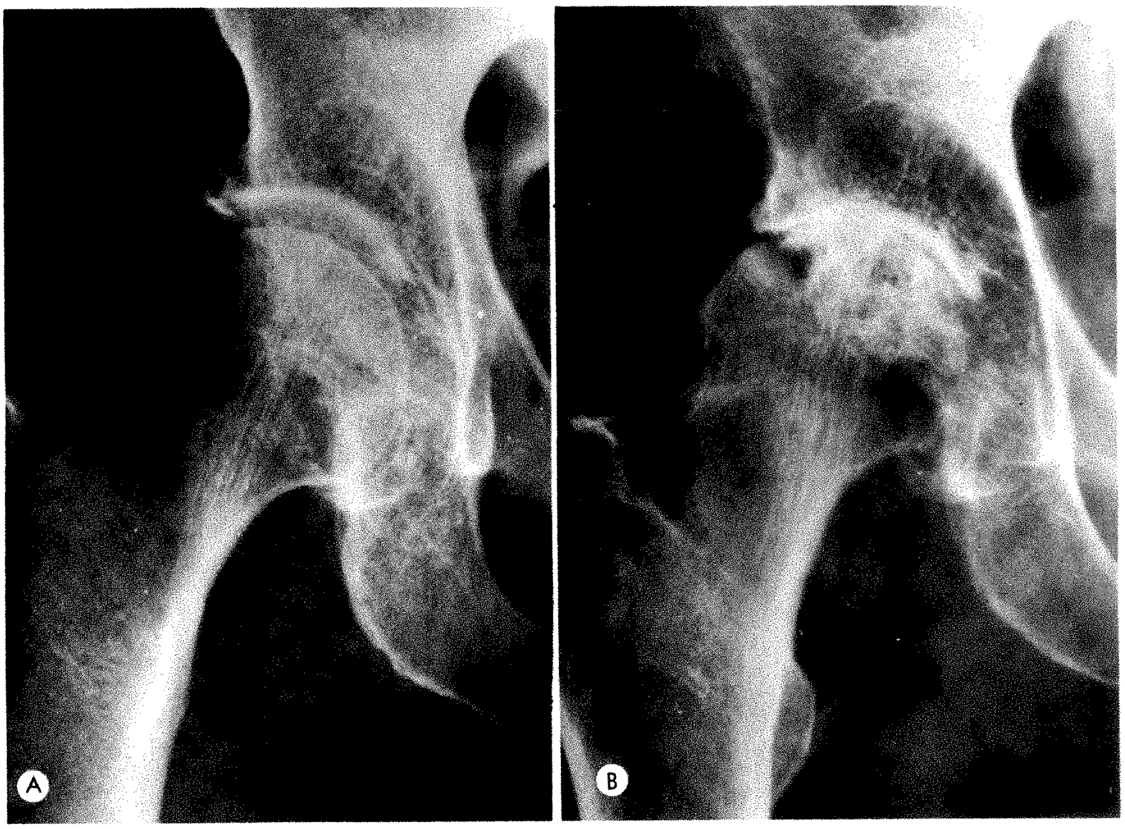

FIG. 4. (*A*) The right hip of a patient with hemochromatosis. Due to superimposition of the acetabulum, it is difficult to ascertain if early articular cartilage calcification is present. There is no joint narrowing. (*B*) One year later, extensive joint narrowing due to cartilage destruction plus sclerosis, cyst formation, and irregular flattening of the femoral head are present. The calcification inferior to the femoral head and lateral to the acetabulum is most likely in the joint capsule. Faint calcification of the symphysis pubis was identified. The left hip is normal. (Courtesy of Dr. Howard L. Steinbach.)

mainder notice joint pain one to several years after the initial symptoms of the disease.[9] Patients in whom the onset of hemochromatosis appears after 50 years of age are more likely to develop arthritis than those who manifest the disease earlier in life.[9,16] An acute inflammatory arthritis may be superimposed on the chronic arthropathy. Chondrocalcinosis is commonly associated with hemochromatosis, occurring in as many as two-thirds of the patients with arthropathy.[9] Calcium pyrophosphate crystals have been demonstrated in the joint effusion in conjunction with an acute inflammatory synovitis.[16]

Serum iron levels are elevated, the serum iron binding capacity is decreased due to the saturation of transferrin, and biopsies demonstrate iron deposition in the liver, gastric mucosa, bone marrow, and skin. Synovial biopsies in untreated patients often show iron in the synovial lining cells.[31,37] Venesection does not prevent the onset or progression of arthritis, probably because the excess iron leaves the synovium more slowly than the other organs of the body.[19] Because idiopathic hemochromatosis is often familial, asymptomatic relatives should be evaluated for this disorder before permanent tissue damage has occurred.

ROENTGENOGRAPHIC FEATURES (Figures 1-5)

The arthritis most commonly involves

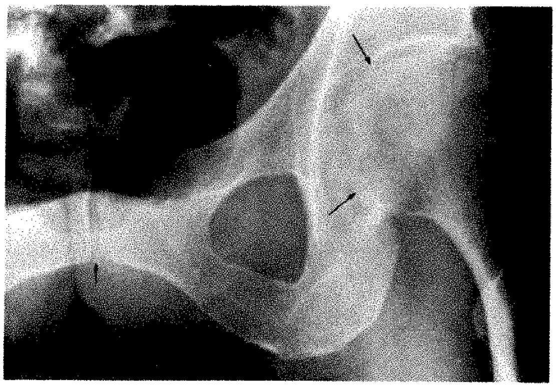

FIG. 5. Calcification in the symphysis pubis plus the articular cartilage of the left hip (arrows). The linear calcification in the articular cartilage parallel to, but separated from, the femoral head which extends lateral to the acetabulum is often more readily identified than the more medial calcification which is superimposed on the acetabulum.

the hands. Small subchondral cyst-like rarefactions located in the metacarpal heads with predilection for the second and third are characteristic lesions. These cysts usually have a fine rim of sclerosis. Frequently uniform cartilage narrowing is also present, particularly when the cyst is observed to communicate with the joint. Actual bony enlargement of the metacarpal heads may also occur.[38] Erosion of the articular surface without cyst formation may be noted. Osteophytes may form in the more severely affected joints but they are usually not a common feature. The carpal and proximal interphalangeal joints may also be affected, the distal interphalangeal joints less commonly so. In contrast to rheumatoid arthritis, there are no marginal erosions, synovial thickening or effusion, ulnar deviation, tendinous insertion lesions, subcutaneous nodules nor acute osteoporosis. Generalized chronic osteoporosis may be present.[9] Wrist involvement consists of cyst-like lesions of the distal ulna and radius and proximal carpals with or without marginal sclerosis. Cartilage narrowing occurs particularly when the cysts are large.

Although the arthritis usually begins in the hands, in the majority of patients it usually progresses to involve the larger joints. The disease in the knees and hips appears similar to osteoarthrosis with cartilage narrowing and marginal osteophyte formation. Subarticular cysts may be present in the femoral heads but are rare in the knees. Sclerosis is uncommon. Rapid destruction of the weight bearing surface and collapse of a femoral head may also occur.[36] Roentgenographic abnormalities are less frequent in the shoulders and elbows, and when present usually consist of minor cyst-like lesions, although considerable sclerosis of subchondral bone with irregularity of the articular surface of the humeral head has been seen.[16]

Chrondrocalcinosis is simultaneously present in about two-thirds of the patients with arthropathy due to hemochromatosis.[9] This finding alone is not specific for hemochromatosis since it can be seen in association with other diseases, as well as in asymptomatic patients.[18] The calcium pyrophosphate dihydrate deposition is similar in appearance to that of idiopathic chondrocalcinosis without hemochromatosis. The knee is most often involved with calcification of the menisci occurring twice as common as the hyaline cartilage. The triangu lar cartilage of the wrist is next in frequency followed by the hip, elbow, symphysis pubis, shoulder and rarely the metacarpophalangeal joints. Calcium pyrophosphate may be deposited in the outer fibers of the annulus fibrosus of the lumbar and cervical spine, the ligamentum flavum of the spine, and in degenerative fissures in the intervertebral disks.[6]

Although chondrocalcinosis is often present at symptomatic joints, the cartilage calcification does not always correspond to the joint symptomatology. Calcium pyrophosphate dihydrate (CPPD) crystals may be demonstrated in symptomatic joints in the absence of roentgenographically demonstrable cartilage calcification, or calcification may be present in asymptomatic joints and not identifiable in the symptomatic joints.[18,26]

DISCUSSION

For many years the arthritis frequently noted in association with hemochromatosis had been attributed to the simultaneous occurrence of degenerative osteoarthrosis or rheumatoid arthritis. Only recently has the arthropathy specific for this disorder been characterized and the significance of the frequently associated chondrocalcinosis recognized.[1,9,16,19,30,38] Localized chondrocalcinosis has been noted in association with many disorders including hemochromatosis. Generalized chondrocalcinosis, defined as calcification of the cartilage of more than two groups of joints, is commonly seen in only two disorders: idiopathic calcium pyrophosphate dihydrate (CPPD) deposition disease, also called the pseudogout syndrome, and hemochromatosis.[18] The presence of chondrocalcinosis plus the arthritis involving the metacarpophalangeal joints, radiocarpal, and proximal interphalangeal joints should alert one to the possibility of CPPD deposition disease which in turn may be associated with hemochromatosis. Predilection for arthritic involvement of the radiocarpal joint in conjunction with the pseudogout syndrome has been demonstrated.[26] Involvement of the metacarpophalangeal joints appears to be more common in hemochromatosis than in the other arthropathies associated with chondrocalinosis.[1]

Chondrocalcinosis plus the demonstrations of CPPD crystals in the aspirate from the symptomatic joint may be simultaneously present. However, cartilage calcification may be noted only in asymptomatic joints, the symptomatic ones lacking roentgenographically demonstrable calcification. CPPD crystals may be demonstrated in the aspirates from symptomatic joints in the absence of visible chondrocalcinosis. Thus, it must be emphasized that the absence of roentgenographically demonstrable cartilage calcification does not exclude the diagnosis of CPPD deposition disease or hemochromatosis.[18,26]

Although the etiology of chondrocalcinosis has not been fully elucidated, it has been suggested that the presence of excess ferrous iron in the joint tissues inhibits the pyrophosphatase enzyme, thereby resulting in the deposition of CPPD crystals in the joint.[21] Divalent cations also alter the biomechanics of the cartilage and may concomitantly lead to the cartilage damage and joint destruction seen in the arthropathy of hemochromatosis.[18,35] Cartilage destruction is a prominent feature of the arthropathy of hemophilia, and recently chondrocalcinosis has been described in association with this condition.[18]

In recent years, a number of patients have been observed to have the arthropathy of hemochromatosis without any of the characteristic clinical features commonly associated with this disorder, a situation which is not surprising since only about one-half of patients with hemochromatosis have complaints referable to liver disease or diabetes mellitus. Hemochromatosis was suspected on the basis of the nature and the roentgenographic features of the arthropathy alone.[13,14] Laboratory studies demonstrated increased serum iron, decreased serum iron binding capacity, hemosiderosis, and in some patients portal fibrosis in addition to the excess iron confirming the diagnosis of hemochromatosis.

It is of critical importance to identify patients with hemochromatosis as early as possible, ideally before irreversible tissue damage has developed. Venesection therapy is very successful since it improves the majority of symptoms in patients with the clinical manifestations of hemochromatosis including those of diabetes mellitus, liver failure, and myocardial decompensation.[10] It may not affect the arthritis. Repeated phlebotomy has resulted in definite increase in the longevity of the patients with hemochromatosis. Venesection is also being used in patients with iron overload who do not manifest irreversible cellular damage. It is believed that the removal of excess iron will prevent the portal fibrosis and cellular damage seen in patients with long-standing iron overload and thereby prevent the development of hemochromatosis and the organ dysfunction associated with this disorder.

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BILIARY ASCARIASIS IN CHILDREN

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ABSTRACT:

The ascaris is a common human parasite and has a world wide distribution. In areas where it is endemic, biliary complications are common. In our locality it occurs mainly in children, presenting with upper abdominal colicky pain usually without jaundice. We have analyzed the positive roentgenological findings of 67 cases which presented in one year. The findings on cholangiography are diagnostic. The worm is seen as a linear translucent filling defect in a dilated common bile duct. Usually it is only faintly outlined by thin tram lines and occasionally there may not be excretion of the contrast material. The attention of radiologists is brought to this condition and the appearances of ascariasis infestation of the intestines are also noted.

THE giant round worm (*Ascaris lumbricoides*) thrives in a moist warm climate. It is particularly prevalent in Africa and the Far East [5,7,10,11,17] and is endemic unless efficient closed sewerage systems are utilized. In Africa it has been conservatively estimated that 60 million people harbor the parasite.[5] The definitive hosts are man and the pig, and in man the adult ascarids mainly inhabit the small intestine.[5,13] Their reproduction rate is formidable and the gravid female may lay up to 200,000 ova per day.[1] The hardy ova can remain viable for many years, so that children are particularly liable to repeated infection from contaminated vegetables, water, and soil.

In Africa, massive ascariasis in children is a common form of intestinal obstruction.[5,10,11] The peak incidence of infestation is between four and eight years and at the Red Cross Children's Hospital, Cape Town, Louw,[11] in 1974, reported that during the period 1958 through 1974, 528 cases of acute abdominal conditions were caused or complicated by ascariasis. They constituted 10–15 percent of all acute abdominal emergencies and were second in frequency only to acute appendicitis. The breakdown of complications in these 528 cases was 351 cases (66 percent) of intestinal obstruction, 148 (25 percent) biliary lesions, 25 cases (five percent) of pancreatitis, two cases (0.5 percent) of acute appendicitis, and two cases (0.5 percent) of primary peritonitis.

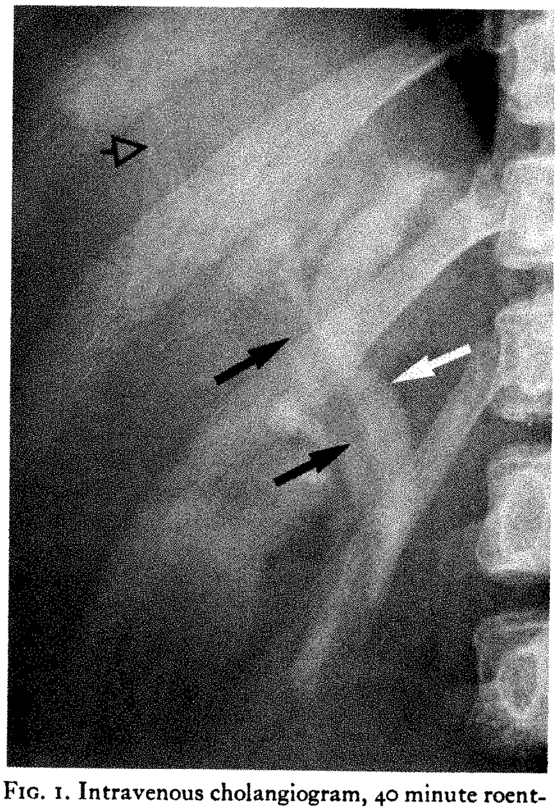

FIG. 1. Intravenous cholangiogram, 40 minute roentgenogram, ascaris (black arrows) in a dilated common bile duct (white arrow). There is also a worm (arrowhead) in the right hepatic duct.

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MATERIAL AND METHOD

An analysis of the roentgenologic records of cases referred from both medical and surgical services during the five year period, 1968 through 1972, showed positive intravenous cholangiographic evidence of biliary ascariasis in 154 cases. After we became more aware of the severity of this problem, the intravenous cholangiograms in children under twelve years of age from all service departments during the year 1974 were reviewed.

There were 126 cases referred because of possible biliary ascariasis. Fifty-nine were considered normal. Sixty-one (48 percent) showed a worm present in the common bile duct. Six (four percent) demonstrated nonfunction, which in conjunction with other clinical or roentgenological evidence of ascariasis infestation, was taken as positive evidence. Therefore a total of 52 percent of the children referred with colicky right upper abdominal pain showed roentgenological evidence of ascariasis. The sex incidence was approximately equal, and the cases consisted of five European, seven African and 56 of mixed parentage. It should be noted that less than ten percent of the children attending this hospital are European. All the proved cases had acute colicky upper abdominal pain, right upper quadrant tenderness, and vomiting. A palpable gallbladder was present in 25 percent of cases.

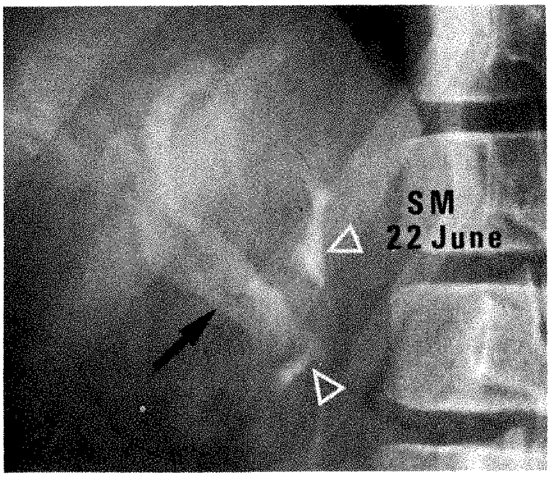

FIG. 2. Intravenous cholangiogram, 40 minute roentgenogram, worm (black arrow) seen in a dilated common bile duct. Contrast material is also present in calyces of kidney (white arrowheads).

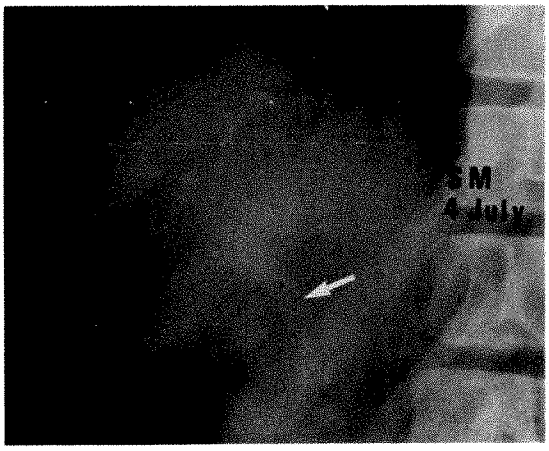

FIG. 3. Intravenous cholangiogram, 40 minute roentgenogram twelve days later, shows a dilated common bile duct (white arrow) but now the worm is absent. No renal excretion was noted.

Cholangiography was performed by an intravenous infusion consisting of 50 percent iodipamide meglumine* in 50 ml of a five percent dextrose solution. This was given by intravenous drip infusion over a period of ten minutes. This method showed better results and was less likely to cause vomiting than a simple intravenous injection. Apart from nausea no complications were encountered. Roentgenograms were taken in the 15° prone oblique position at 20 minute intervals. A worm was usually seen as a large lucent filling defect contained inside a dilated common bile duct (Fig. 1). Identification in many cases was not always so obvious and a more frequent appearance was two parallel lines of contrast material outlining the worm (unfortunately too faint to reproduce photographically). Tomography was used only if the appearances were equivocal after the 40 minute film. With experience this was not usually necessary. The worms were frequently multiple and sometimes were also present in the major intrahepatic ducts. When a dilated duct containing a worm was

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* Biligrafin forte (Schering A. G.) 20 ml ampule.

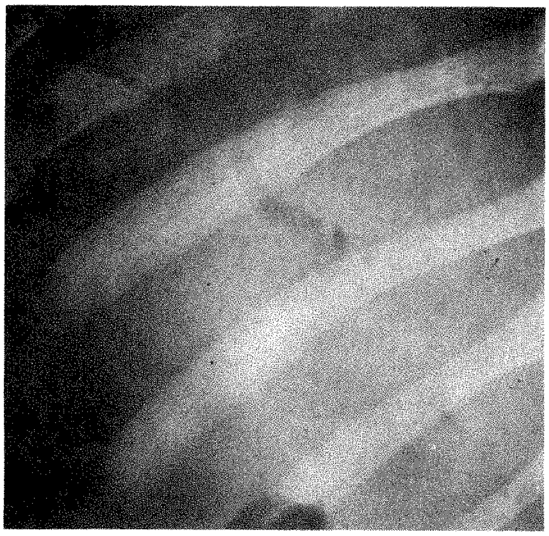

FIG. 4. Intravenous control roentgenogram. Gas is seen in the biliary tree.

seen, medical treatment was instituted and the intravenous cholangiogram repeated after one week. With successful treatment, the worm disappeared, although the duct frequently remained dilated (Fig. 2; and 3).

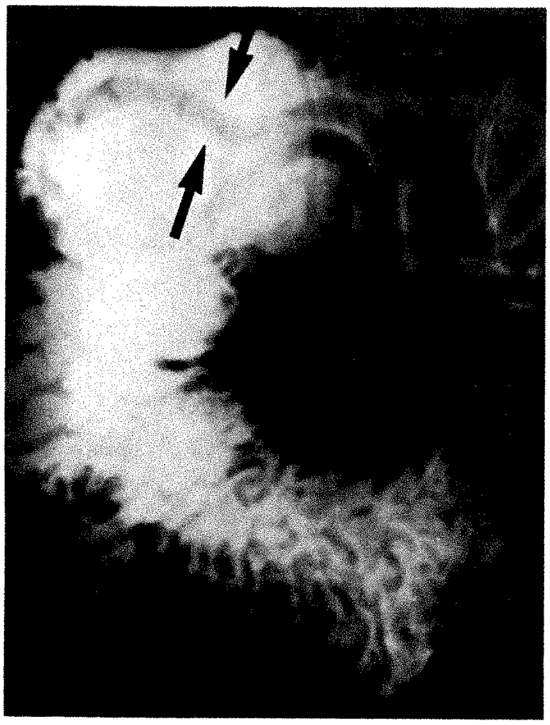

FIG. 5. Barium meal taken during an intravenous cholangiogram demonstrating ascariasis (black arrows) in the first part of the duodenum.

In cases with a partial blockage of the duct by a worm, it was commonly noted that there was a more marked excretion of contrast material by the kidneys (Fig. 2) than when the worm had been passed (Fig. 3). The calyceal pattern of kidney excretion in the oblique roentgenograms may easily be confused with the faint biliary duct "tram lines" of worm obstruction. In one case of partial biliary obstruction, contrast material was seen in both alimentary tract and renal calyces three days after the initial injection. In none of the cases was an ascaris identified in the gallbladder.

Infrequently gas was noted in the biliary system in the control roentgenogram (Fig. 4), and it was noted only once during this series. On six occasions when worms were seen in the common bile duct during the intravenous cholangiogram, an immediate barium meal examination was performed. In all cases worms were present in the duodenum (Fig. 5) and although the dilated common bile duct caused an indentation on the duodenum, the ascarid protruding through the ampulla of Vater was not visualized. This has, however, been noted on endoscopy (Fig. 6).

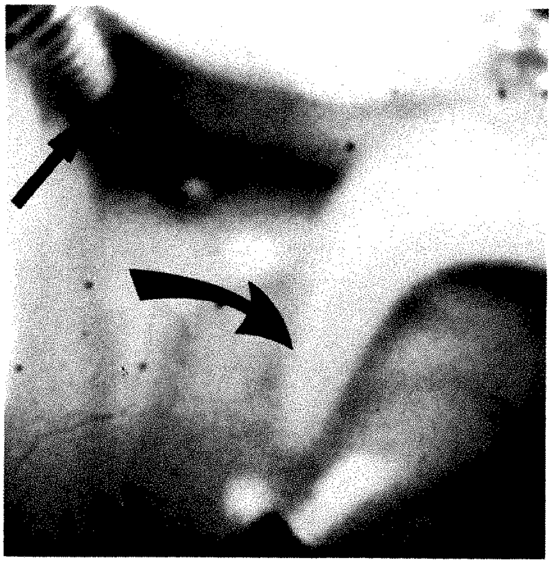

FIG. 6. Photograph taken through endoscope (straight arrow) showing worm (curved arrow) protruding through the ampulla of Vater.

The cases were treated primarily by medical methods that consisted of sedation, intestinal decompression, intravenous fluids, antispasmodics, and anthelminthics. Surgery was resorted to only when repeated intravenous cholangiograms showed a dilated common bile duct or the continued presence of worms. In these cases either duct stricture or death of an incarcerated worm was considered likely. Medical treatment of at least three weeks is advisable before surgery should be considered.[11] When massive infestation of worms or stricture were indications for surgery, operative cholangiography and postoperative T-tube cholangiography were employed. Figure 7 shows an operative cholangiogram in which 80 ascaris were removed at surgery. A subsequent T-tube cholangiogram one week later (Fig. 8) still showed multiple worms present.

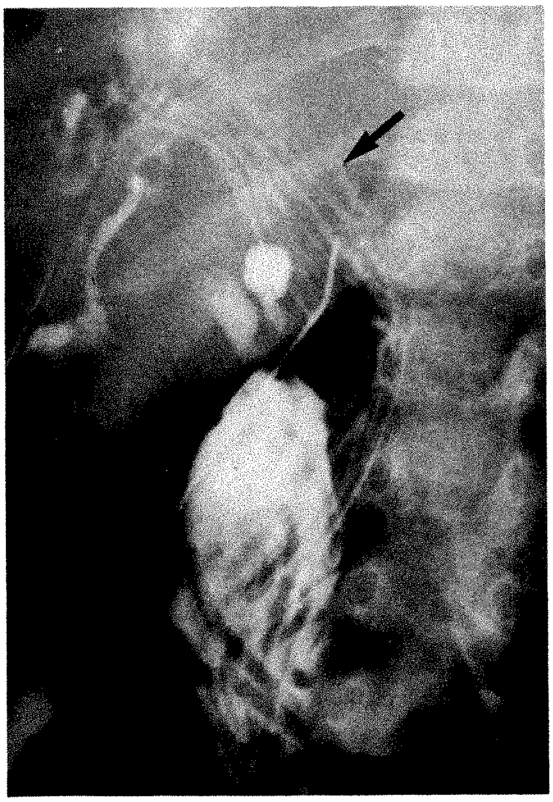

FIG. 7. Operative cholangiogram showing multiple ascarids in a grossly dilated common bile duct (black arrow). The contrast material has passed through into the dilated duodenum which also contains ascarids.

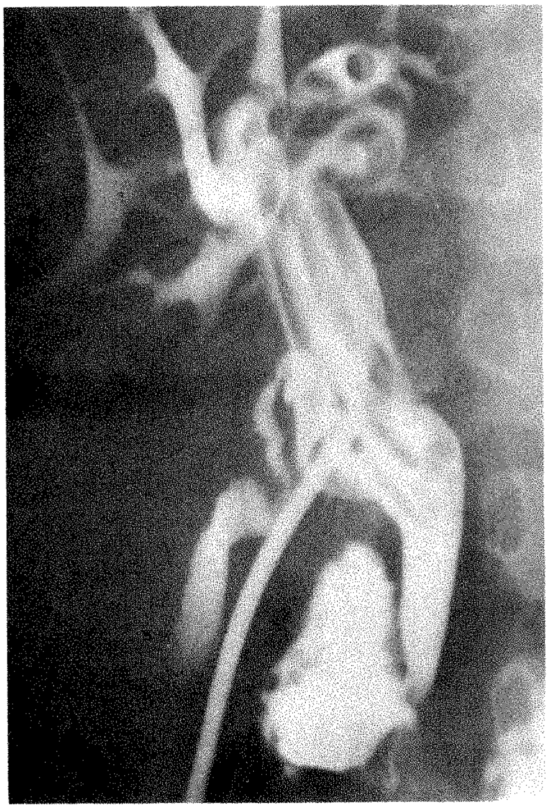

FIG. 8. T-tube cholangiogram showing multiple worms still present after surgery.

DISCUSSION

In our locality, ascaris infestation of the biliary tract is predominantly a disease of children, and during the year 1974 only one adult case was reported at the adjacent Groote Schuur Hospital. It may, however, affect any age group, and a peak incidence between 20–50 years with a slight female preponderance has been reported.[7] The roentgenological appearances of biliary ascariasis, although not widely known to radiologists, have been previously reported.[2,4,5,10–12]

Clinically, jaundice is not a feature of the condition, as the intermittent spasm of the sphincter of Oddi allows bile to escape into the alimentary tract. In Louw's[11] series, 16 percent had a raised serum bilirubin level

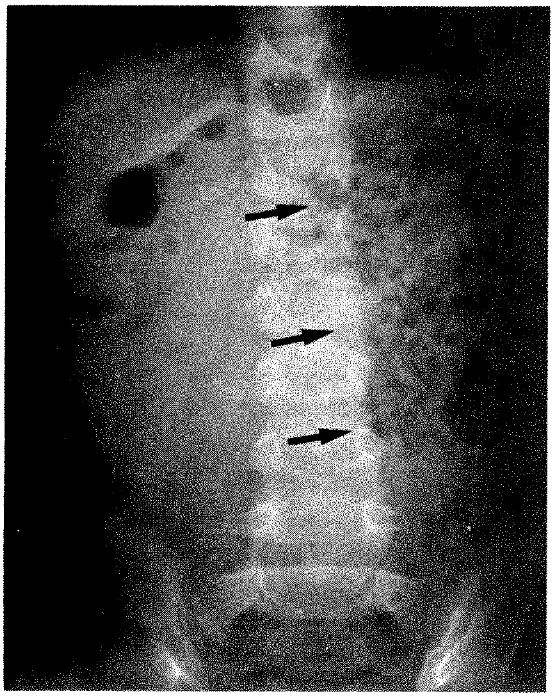

FIG. 9. "Whirlpool" effect of multiple ascarids in the small bowel (arrows). The fluid levels in the small intestine indicate obstruction.

and 26 percent had raised serum amylase levels. A raised serum amylase level may occur whenever the pressure in the pancreatic duct is elevated. During the year under review we were unable to correlate this evidence with definite cases of pancreatitis. The reported complications include acute cholangitis, cholecystitis, stricture with stone formation, perforation of the duct with biliary peritonitis, liver abscess, hepatitis, and pancreatitis.[7,8,10,11,16]

The occasional appearance of ascariasis during a gastrointestinal series is well known to radiologists, and the worm body may either be outlined by barium or show barium inside the lumen of its gut.[1]

In areas where ascariasis is endemic the plain roentgenographic appearances are typical. A report by Issacs[9] from Florida, noted the whirlpool effect of massive infestation (Fig. 9). Obstructive fluid levels in the small intestine are also a feature, and a massive bolus may cause obstruction by its physical size, or may cause volvulus, intussusception or ileocecal spasm. The worm bolus also may cause necrosis of the bowel wall with resulting peritonitis. During this series one case of perforation leading to free intra-abdominal gas occurred. It is also possible to identify a single ascarid when it appears as a tubular density outlined by the gas in the distended small intestine (Fig. 10). An associated unreported feature is the swollen valvulae conniventes that give a "cog wheel" effect to the mucosa (Fig. 11). Recognition of these roentgenographic features is important, so that patients with upper abdominal pain may be examined by intravenous cholangiography to exclude biliary infestation. It should be noted that biliary ascariasis should not be confused[14] with an entirely different biliary parasite, the *Clonorchis sinensis*, a pin-like fluke whose host is fresh water fish, and which is endemic in areas such as Singapore and Hong Kong.[2,6]

It is only in the last 15 years that we have become aware of the frequency of biliary ascariasis in endemic areas. The purpose of this report is to draw the attention of clinicians to the value of intravenous cholangiography as a safe and diagnostic procedure. It may also serve as a warning that in these days of rapid jet transport, recent arrivals from areas such as the Middle East (Israel),[14] Far East (Japan,[8] China,[17] Saigon,[12] Phillipines,[7] and India[13,15]), South America[3] and Africa,[5,10,11] who have unexplained "cholecystitis" without jaundice

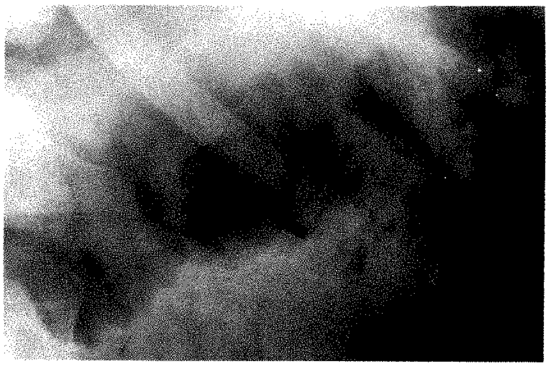

FIG. 10. Single ascarid (black arrow) seen in a dilated loop of small bowel.

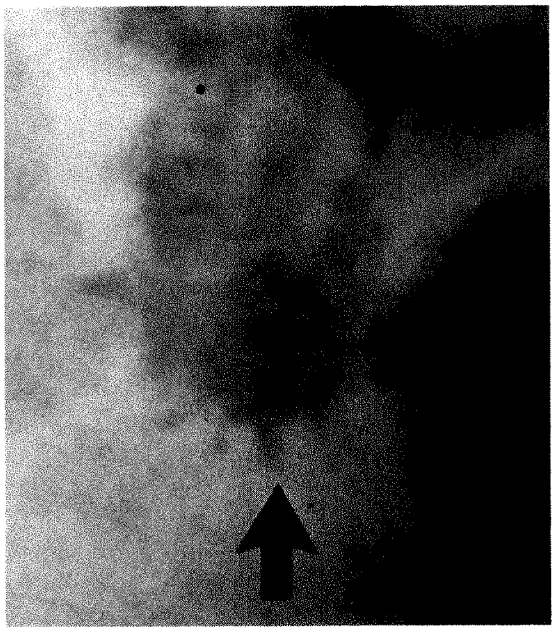

FIG. 11. "Cog-wheel" (arrow) effect of edematous valvulae conniventes.

may be suspected of having biliary ascariasis.

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Acknowledgment is given for the use of Figure 6 to Dr. B. Novis (endoscopist) and for Figure 7 and 8 to Dr. R. Kottler (radiologist) both from Groote Schuur Hospital, Cape Town.

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INTESTINAL MALROTATION IN ADULTS*

ROENTGENOGRAPHIC ASSESSMENT WITH EMPHASIS ON ISOLATED COMPLETE AND PARTIAL NONROTATIONS

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ABSTRACT:

Intestinal malrotation may occur as an isolated deformity. It may involve either the proximal (duodenojejunal) or the distal (cecocolic) intestinal segment. A survey of 28 consecutive cases of rotational abnormalities in the adult population demonstrates a diversity of roentgenographic presentations. Twelve cases exhibited the classical form of nonrotation of the entire midgut. The rest showed isolated forms of complete and partial rotations as well as a variety of intermediary forms previously not reported in the literature. Familiarization with this concept avoids confusing interpretations and errors in the roentgenographic diagnosis.

MOST of the clinical emergencies related to congenital malrotation of the midgut are encountered in the neonate. Kiesewetter and Smith[3] reported a 55 percent incidence in the first week and an 80 percent incidence in the first month of life. Their roentgenographic diagnosis, prognosis and treatment have been discussed in the literature.[3,5–8,11] The association of peritoneal bands (Ladd's bands) and faulty fixation of the mesentery leading to midgut volvulus has been previously stressed.[11]

Most of the midgut malrotations, however, are seen in asymptomatic patients and are diagnosed only accidentally later in life. It is nevertheless important to recognize correctly and promptly such abnormalities. Patients with unexplained abdominal complaints, directly related to anomalies of intestinal rotation may present themselves later in life.[2,3,9] The symptomatology in this group of patients is ill-defined, long standing, and intermittent. Often, roentgenographic examinations performed in a period of clinical remission are unremarkable except for the presence of a congenital abnormality. The recognition of such an anomaly and of its implications is evident. Secondly, lack of understanding of the mechanism of the normal development of the midgut may lead to unusual and confusing interpretations and to errors in the roentgenological diagnosis.

For a number of years I have been impressed by the unusual variety of roentgenographic presentations of abnormalities of rotation in the adult population. I believe that they are more common than generally thought and that only the confusing diversity of appearances prevents their identification.

A review of the pertinent literature together with roentgenographic observations based on an analysis of 28 cases, forms the basis of this communication.

BACKGROUND

The herniation of the midgut into the umbilical cord and its complicated return to the abdominal cavity as part of the normal embryologic development, were described by Meckel and Mall, at the end of the 19th century.[5]

In 1923, Dott[1] outlined and classified the anomalies of intestinal rotation and mesenteric fixation. He arbitrarily divided the developmental process into three stages, and described the congenital anomalies related to these stages of evolution. Abnormalities of his second stage of rotation, called "malrotations," were further separated into those resulting from an absence of the normal rotational process (failure of rotation) and those related to abnormal rotations (reversed rotation). The former group constitutes the vast majority of the malrotational abnormalities, and is the subject of this presentation.

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As long ago as 1898, Mall,[10] examining human embryos, mentioned that the return of the intestine from the umbilical cord must be rapid and total since embryos 40 mm long show the small bowel either totally within the cord or completely re-

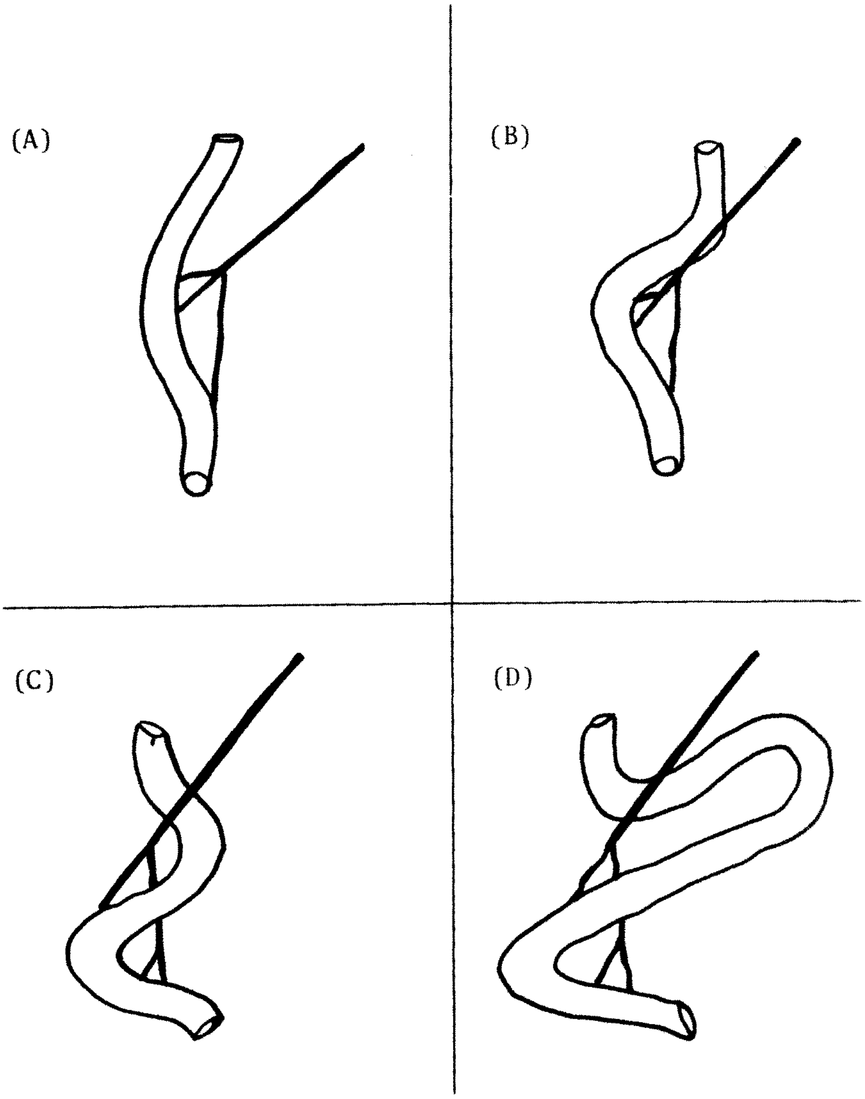

FIG. 1. The intermediate stages of development of the duodenojejunal loop. (After Snyder and Chaffin.) (*A*) Zero-degree rotation. The midgut is located in front of the superior mesenteric artery (SMA) with a slight bulge in its middle one-third. (*B*) Ninety-degree rotation. The proximal loop moves downward and to the right of the SMA attempting to slide under it. (*C*) One hundred and eighty-degree rotation. Continuous movement towards the left under the SMA. Duodenojejunal junction is now located at the left of the SMA. (*D*) Two hundred and seventy-degree rotation. The rotational process is completed by a continuous move, cephalad and towards the left of the SMA. The duodenal sweep is now completely developed and the attachment of its dorsal mesentery to the posterior abdominal wall follows.

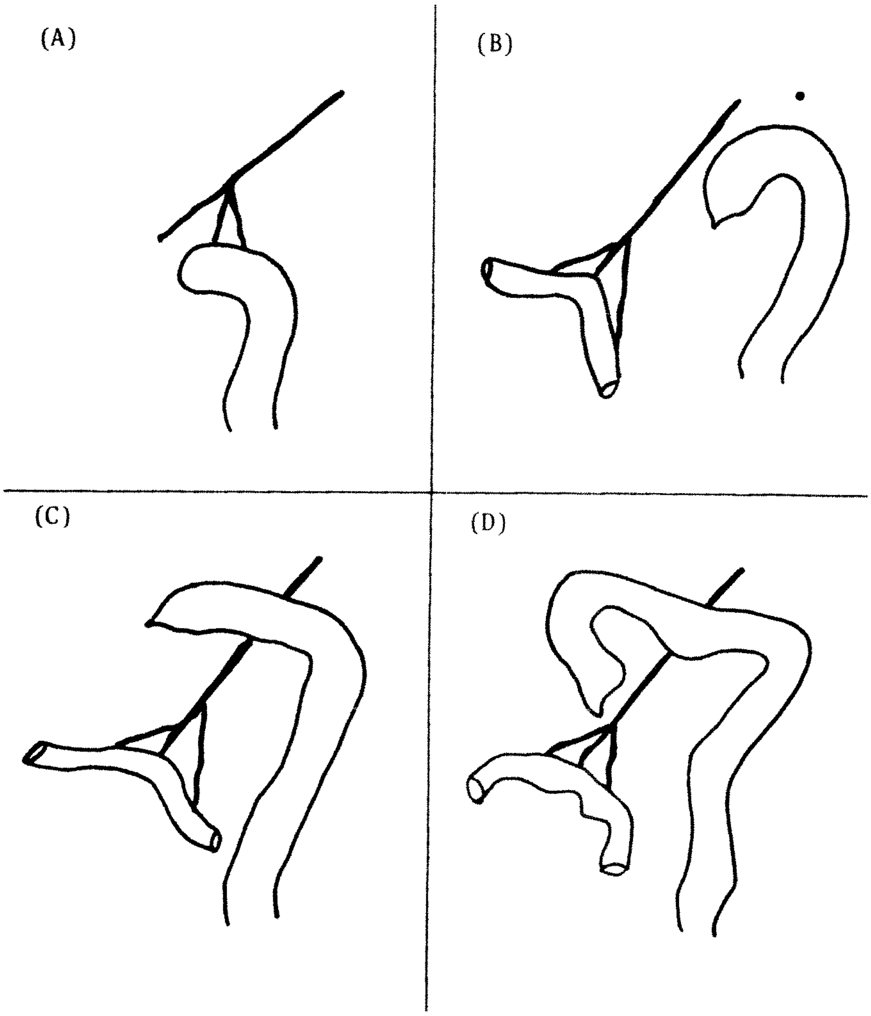

Fig. 2. The intermediate stages of development of the cecocolic loop. (After Snyder and Chaffin.) (*A*) Zero-degree rotation. Before the rotational process starts the distal loop is located beneath the SMA. (*B*) Ninety-degree rotation. The cecocolic loop moves cephalad and to the left of the SMA. (*C*) One hundred and eighty-degree rotation. Movement continues toward the right side over the SMA. (*D*) Two hundred and seventy-degree rotation. The rotational process is completed by a continuous move to the right of the SMA. The growth of the colon brings the cecum into the right lower quadrant. The fixation of the dorsal mesocolon to the posterior abdominal wall follows.

turned to the abdominal cavity.

The concept of a rapid rotation of the midgut and of the simultaneous and complete return to the abdominal cavity was common knowledge which persists to the present day. According to this concept, cases of failure of rotation will involve the entire midgut and a classical and severe malposition will result; the small bowel located in the right and the colon in the left side of the peritoneal cavity.

Several other investigators, however, noticed that the process of rotation and return is, in reality, composed of a multitude of intermediate stages of development.[10] Snyder and Chaffin,[9] after studying 50 human embryos (four–12 weeks' gestation) emphasized the significance of the duodenojejunal segment and of the cecocolic segment in the normal and abnormal developmental process. Their description represents a significant achievement since it helped explain and clarify a variety of confusing clinical and roentgenographic presentations.

ROTATION OF THE DUODENOJEJUNAL LOOP (Fig. 1)

In a 5 mm embryo (fourth week of gestation), the primitive intestinal tract is a straight tubular structure with a slight anterior curve in its middle third. The superior mesenteric artery (SMA) comes from the posterior abdominal wall to the center of the bulge (Fig. 1*A*) and its distribution defines the length of the midgut (middle third of the duodenum to the distal transverse colon). At the fifth week of gestation, the fast growing intestine herniates into the umbilical cord. The counterclockwise rotation of the duodenojejunal loop takes place around the axis of the SMA and can be separated into three distinct intermediate stages.

1. *Ninety-degree Rotation*, fifth week of gestation (10 mm embryo). The duodenojejunal segment has been pressed down, inferior and to the right of the SMA presumably by the developing liver (Fig. 1*B*).
2. *One Hundred and Eighty-degree Rotation*, eighth week (25 mm embryo). The proximal loop has passed beneath the SMA and the duodenojejunal flexure is located now slightly to its left (Fig. 1*C*).
3. *Two Hundred and Seventy-degree Rotation*, tenth week (40 mm embryo). The small bowel with proximal jejunum as its leading segment, returns to the abdominal cavity and pushes the fourth portion of the duodenum cephalad and to the left of the SMA, completing the rotational process (Fig. 1*D*). This last stage of rotation takes place in the abdominal cavity at the time when the cecocolic loop is still located within the cord. The return of the distal segment begins.

ROTATION OF THE CECOCOLIC LOOP (Fig. 2)

At the fourth week of gestation before the rotational process starts (5 mm embryo) the cecocolic loop is located beneath the SMA (Fig. 2*A*).

Ninety-degree Rotation, fifth week (10 mm embryo). The distal loop moves from beneath to the left of the SMA (Fig. 2*B*).

One Hundred and Eighty-degree Rotation. The cecum drops in the abdominal cavity at the tenth week (40 mm embryo), still positioned to the left of the SMA. It starts moving over the artery in a superior and anterior direction (Fig. 2*C*).

Two Hundred and Seventy-degree Rotation. The completion of the rotation is accomplished shortly after the tenth week by a continuous move to the right of the SMA (Fig. 2*D*). Most of the rotation of the distal loop takes place in the abdominal cavity and is followed by the attachment of the mesentery of the small bowel and colon to the posterior abdominal wall.

DISCUSSION

In their original presentation Snyder and Chaffin[9] pointed out that the "urge" of rotation is first evident in the proximal seg-

Table I

MALROTATION OF THE MIDGUT IN THE ADULT POPULATION: 28 CASES

Type of Abnormality	No. of Cases
Complete failure of rotation of the proximal and distal loops	12
Complete failure of rotation of the proximal loop and partial rotation of distal loop	2
Complete failure of rotation of the proximal loop and normal rotation of the distal loop	7
Partial failure of rotation of the proximal loop and complete nonrotation of the distal loop	2
Partial failure of rotation of the proximal loop and normal rotation of the distal loop	3
Normal rotation of proximal loop and partial rotation of the distal loop	2

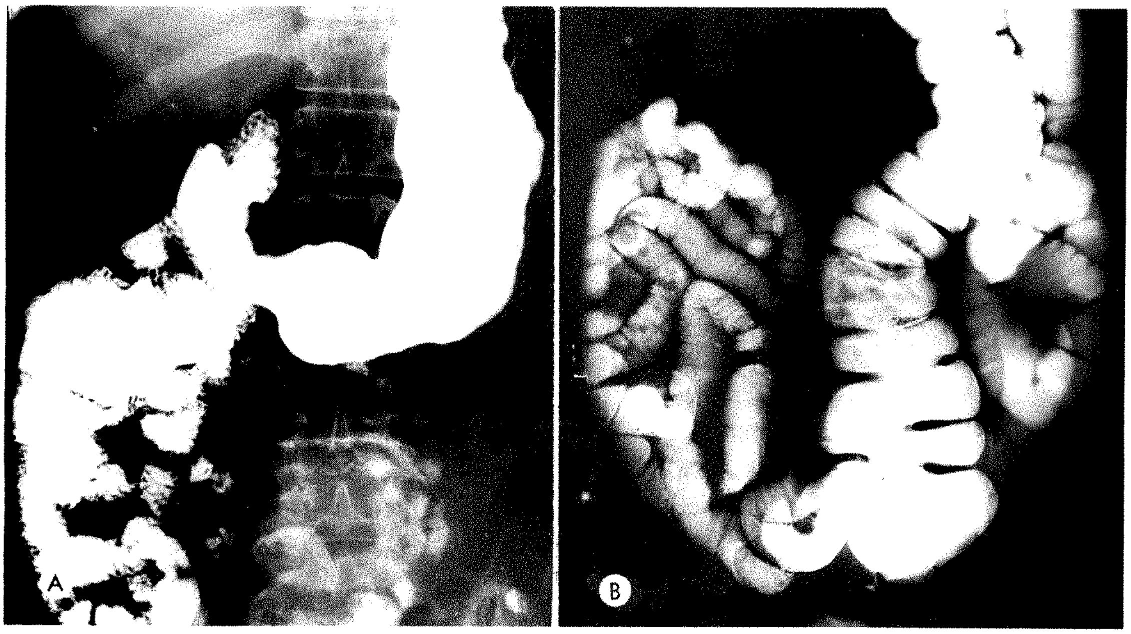

Fig. 3. Classical presentation of nonrotation of both loops. A 49 year old female admitted for rectal bleeding. (*A*) An upper gastrointestinal examination prone roentgenogram, demonstrates complete nonrotation of the proximal segment. The duodenal loop does not cross over but enters the proximal jejunum on the right side of the spine. (*B*) A barium enema examination prone roentgenogram. The colon is located on the left side of the spine with the cecum in the pelvis. The terminal ileum in the right abdomen enters the cecum from its right posterior aspect.

ment; an arrest in its motion probably sets the stage for nonrotation of the distal segment. It was implied, therefore, that in the majority of cases, failure of rotation of the proximal segment is accompanied by nonrotation of the distal segment. On the other hand, the potential of malrotational abnormalities to occur in an isolated form at any stage in either or both loops was stated. Documentation of this concept was made in 1966 when Lewis[4] presented four cases of duodenal obstruction associated with incomplete duodenal rotation and normally positioned colon. This point was further emphasized recently by Firor and Harris[2] with the publication of three similar additional cases. They are important contributions because they document the coexistence of isolated incomplete duodenal rotation in the presence of a complete rotation of the colon. In addition, they demonstrate the clinical potential of such abnormalities to produce partial duodenal obstruction not only in the neonate but later in life. They have been found to be associated with faulty mesenteric fixation where the duodenum is angulated, kinked and compressed by adhesions, and where surgical correction is followed by uneventful recovery.

Over the last five years I have accumulated 28 consecutive cases of malrotation of the midgut. The diversity of roentgenographic presentations is impressive and according to the old concepts, surprising. To simplify, they can be divided into complete or partial failure of rotation and into abnormalities affecting the proximal segment (duodenojejunal loop), the distal segment (cecocolic loop) or both (Table I). The partial failure of rotation refers to attempted but incomplete rotation usually around 90° to 180° (Fig. 1; and 2). In twelve of the cases, the classical, complete nonrotation of the proximal and distal segments is evident (Fig. 3). Nine of the cases, however, show complete or partial nonrotation of the proximal loop with normal rotation of

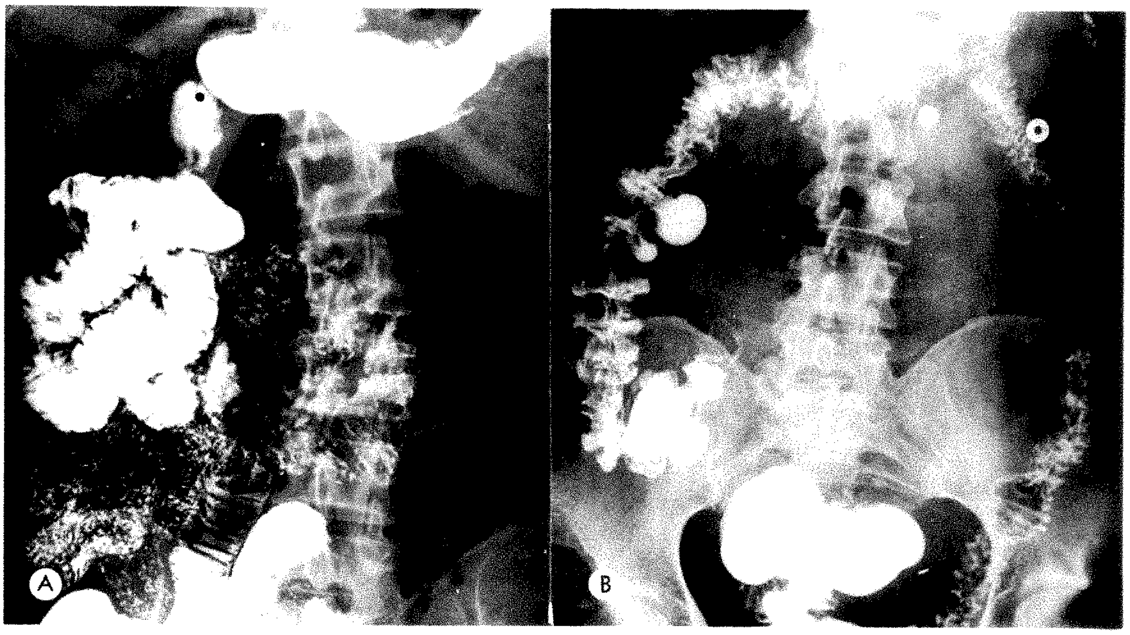

FIG. 4. Complete nonrotation of the proximal loop and normal rotation of the colon. A 43 year old female with gastric ulcer. (*A*) An upper gastrointestinal examination. The complete nonrotation of the proximal segment is evident. (*B*) Same patient. Barium enema examination postevacuation roentgenogram. The colon (distal segment) is normally rotated.

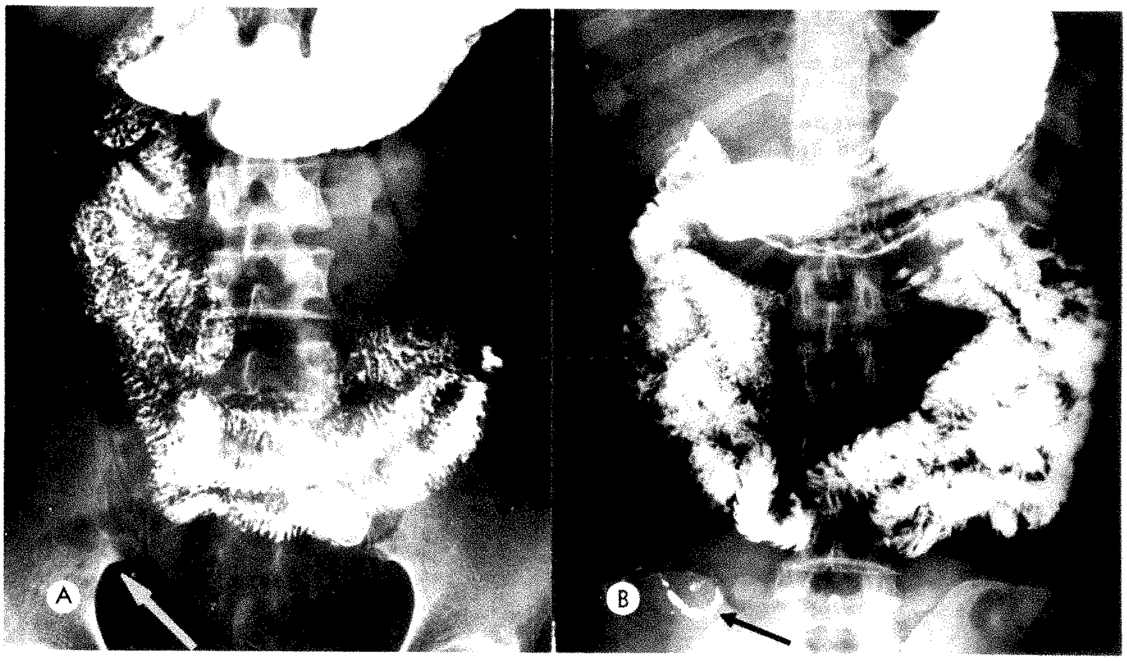

FIG. 5. Complete nonrotation of the proximal loop and normal rotation of the colon. (*A*) A 33 year old male. Upper gastrointestinal examination demonstrates complete nonrotation of the proximal segment. The colon is in normal position. Feces in the right lower quadrant show the position of the cecum (arrow). (*B*) A 37 year old male with epigastric pain. An upper gastrointestinal examination. The duodenum and proximal jejunum are on the right side of the spine. The intestine located on the left is the distal jejunum. Previous barium enema examination showed a normal positioned colon. Feces in the right colon and residual barium in a normally located appendix (arrow) are seen.

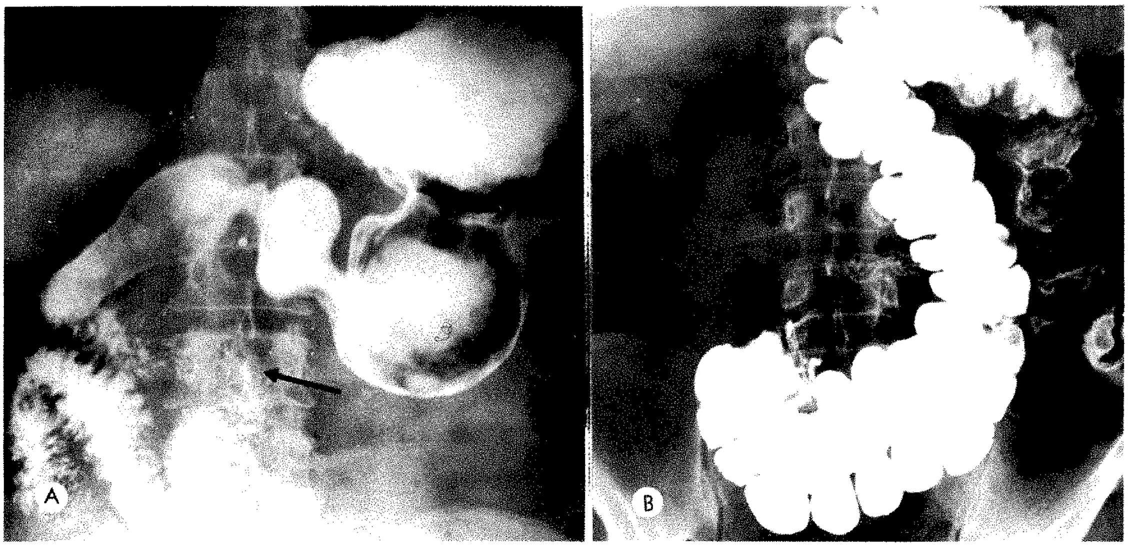

FIG. 6. Partial rotation of the proximal segment and nonrotation of the distal segment. (*A*) Upper gastrointestinal examination demonstrates an incompletely rotated duodenal loop with the duodenojejunal junction overlapping the spine (arrow); 90° rotation. (*B*) The colon shows nonrotation. There is only a timid and unsuccessful attempt at rotation, with the transverse colon partially overriding the spine.

the colon (Fig. 4–6). Other expected but less common variations such as nonrotation of the proximal loop associated with partial rotation of the distal loop (Fig. 7; and 8), partial rotation of the proximal loop associated with malrotation of the distal loop (Fig. 9), and normally rotated proximal loop accompanied by partially rotated distal loop can be seen (Fig. 10). To the best of my knowledge these last forms of malrotations have not been previously discussed and illustrated in the literature.

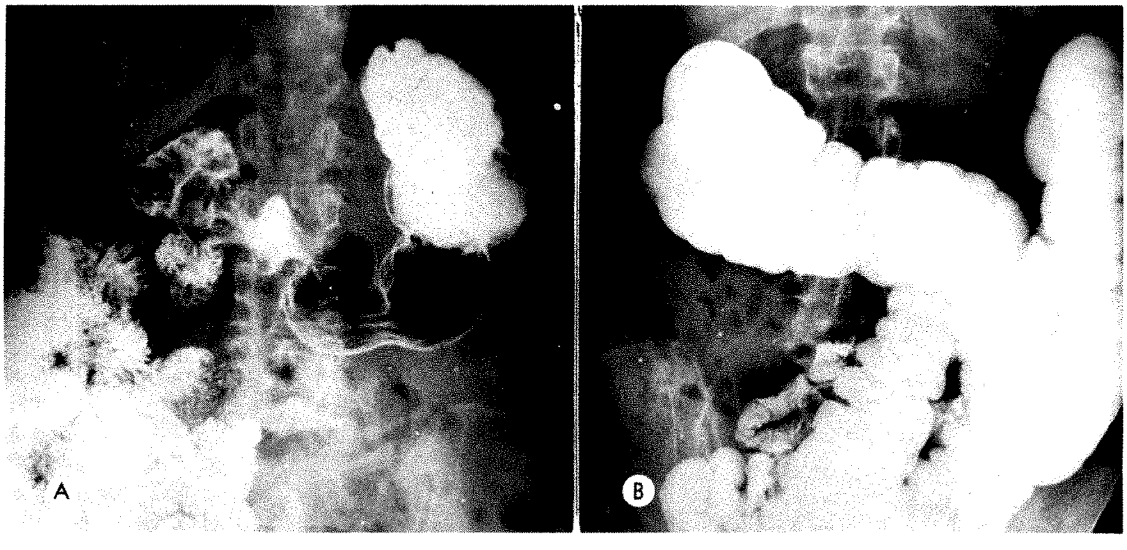

FIG. 7. Nonrotation of the proximal loop and partial rotation of the distal loop. (*A*) Upper gastrointestinal examination demonstrates the complete nonrotation of the proximal loop. (*B*) Barium enema examination shows the colon crossing over the spine but returning in the left lower quadrant. The rotational process of the distal segment is about 180°, therefore incomplete.

Although the series is relatively small, certain generalizations can be made. The isolated forms of partial or total midgut malrotation as well as transitory forms do occur and can be easily recognized roentgenographically. They represent a significant number of the total cases of malrotation observed on routine barium examinations. An infinite number of intermediary forms can be expected to exhibit a variety of roentgenographic presentations, from partial to total nonrotation affecting independently or together the proximal or distal loop, or both.

It is obvious that the evaluation of a rotational abnormality should always include an examination of the upper as well as of the lower gastrointestinal tract. The mere presence of jejunal loops in the right upper quadrant should not be automatically considered a congenital aberration. Jejunal loops may be located in the right upper quadrant as a consequence of mesenteric redundancy, acquired right-sided duodenal hernia, previous surgical procedures, adhesions, left-sided abdominal masses, etc. The visualization of the entire duodenal loop and of the duodenojejunal junction is crucial in this evaluation. Since the main trunk of the SMA projects over the upper lumbar vertebral bodies, the presence of a duodenojejunal junction at the left side of the spine indicates a complete rotation of the proximal loop; its presence over the spine indicates a partial rotation (90°–180°), and its location at the right of the spine indicates nonrotation. Although the normal location of the duodenojejunal junction may vary in the vertical axis (average L1–L2), it is almost always found to the left of the spine. In 100 consecutive cases without rotational abnormalities observed in our department, only four showed a slight variation from this rule with the duodenojejunal junction overlapping the left side of the spine.

In the roentgenographic evaluation of the distal loop, the presence of the entire colon to the left of the spine with the cecum

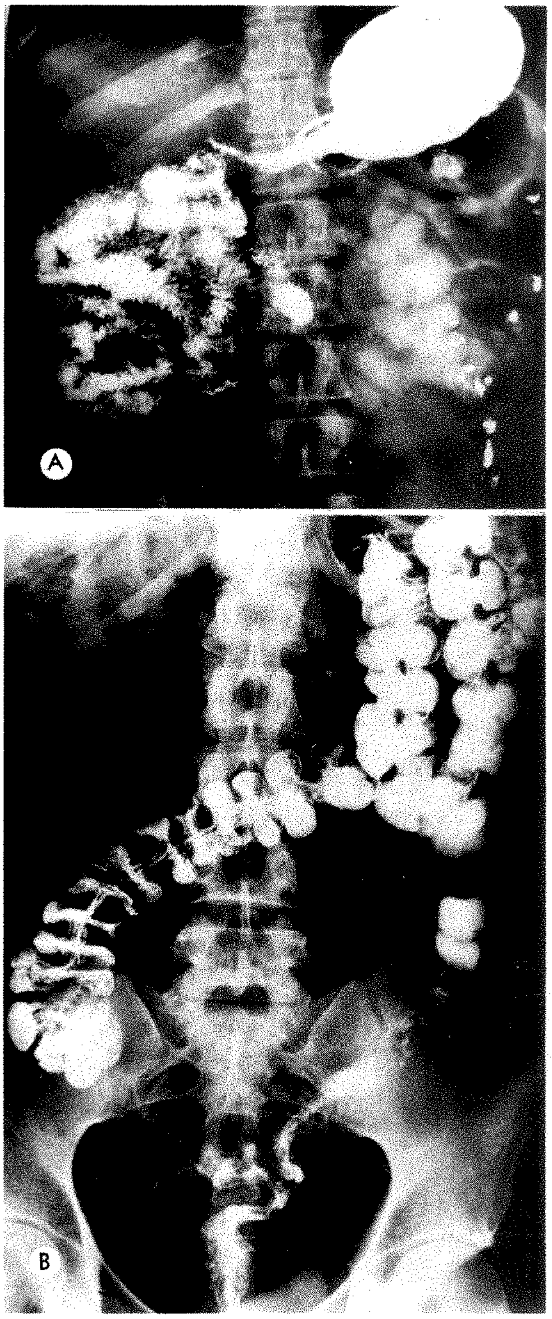

FIG. 8. Nonrotation of the proximal loop and partial rotation of the distal loop. (*A*) Upper gastrointestinal examination shows nonrotation of the proximal segment. (*B*) The colon is incompletely rotated. The original rotational process did not take place since the transverse colon is situated on the left side of the spine. The ascending colon however, crosses the spine farther down (not above the SMA) bringing the cecum into the right lower quadrant.

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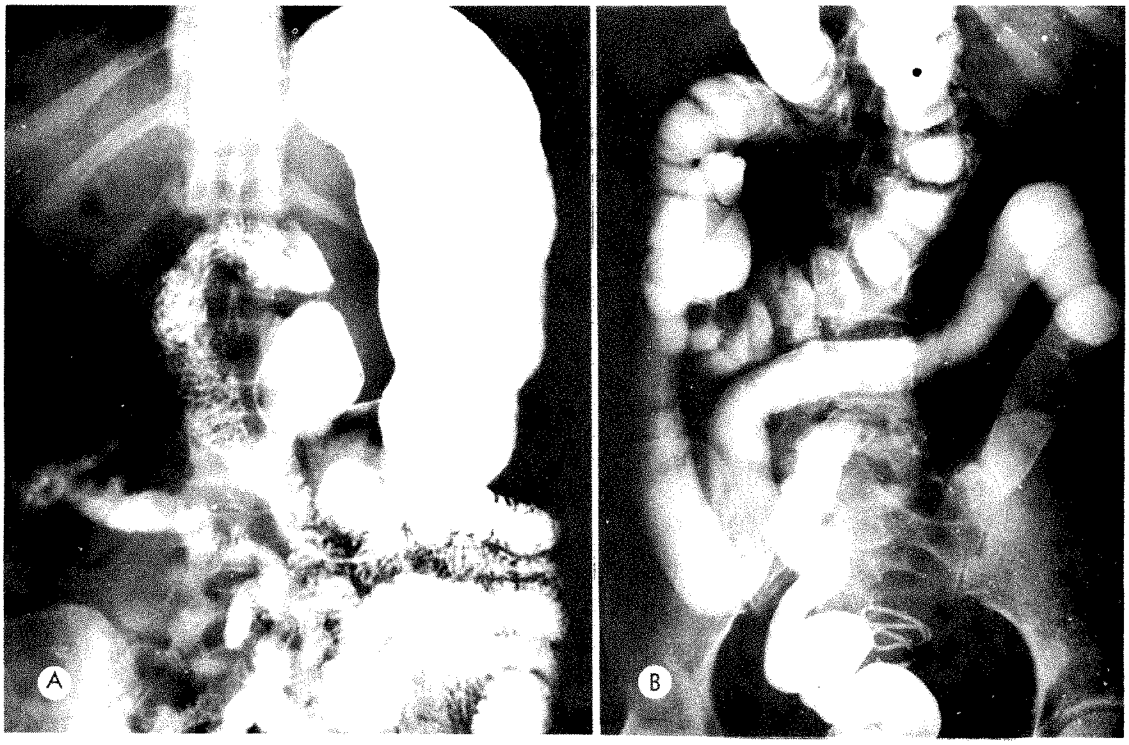

Fig. 9. Partial rotation of the proximal loop and nonrotation of the distal loop. A 23 year old female with pelvic pain. (*A*) Upper gastrointestinal examination shows a rotation of about 180° of the proximal loop. Note duodenum crossing the spine and entering the jejunum in the left upper quadrant. The fourth duodenal segment and the normal duodenojejunal junction are not developed. (*B*) Barium enema examination demonstrates a nonrotated colon. The mid-line position and configuration of this peculiar colon is most likely secondary to the persistence of a primitive dorsal mesentery. Anomalies of fixation are commonly associated with malrotational abnormalities.

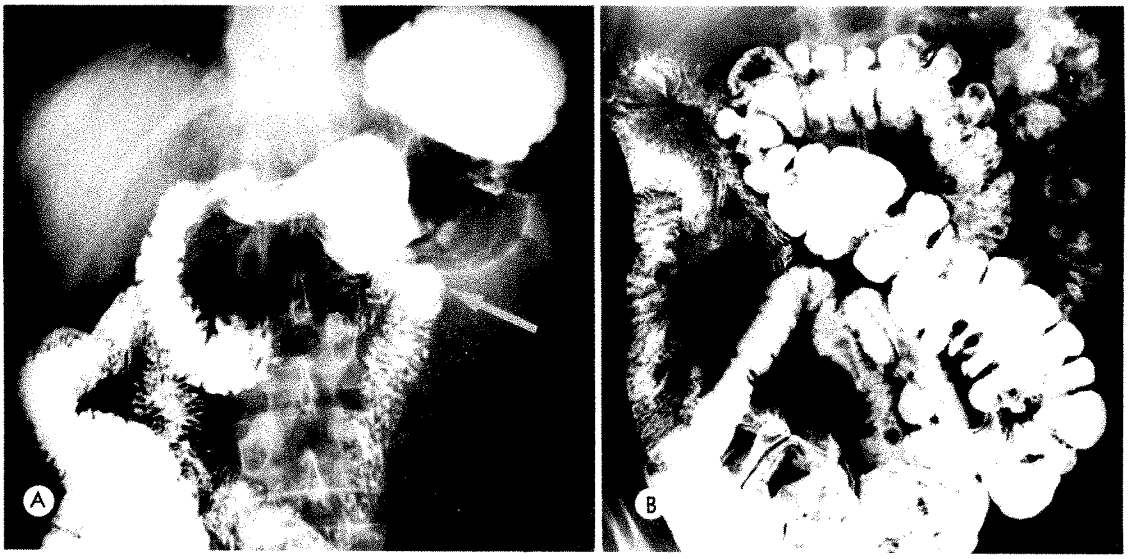

Fig. 10. Normal rotation of the proximal loop with partial rotation of the distal loop. (*A*) Upper gastrointestinal examination shows normal rotation of the duodenal loop with the duodenojejunal junction on the left side of the spine (arrow). (*B*) A delayed follow-up roentgenogram demonstrates an attempted but incomplete rotation of the distal segment. Note the colon crossing the spine but returning in the left lower quadrant.

either in the mid-abdomen or pelvis indicates nonrotation while different degrees of partial crossings of the colon over the spine indicate attempted but incomplete rotation. Unless both of these segments are clearly demonstrated on roentgenographic examinations, a comprehensive evaluation cannot be made. Lack of familiarization with the concept of isolated, complete, or partial rotation of the midgut accounts for the confusing statements and erroneous diagnoses made in these cases.

CONCLUSIONS

Abnormalities of rotation represent a complex group of congenital anomalies that exhibit a wide variety of roentgenographic presentations. They may involve the entire midgut or may be segmental, affecting only the proximal or distal loop. In addition, forms of transition consisting of partial rotation of one or both loops are seen.

The isolated, segmental malrotation and the intermediary forms are frequent findings that can be explained by deviation from the normal developmental process. They constitute the majority of cases observed in this series.

Their clinical significance is similar to that of the complete form of malrotation. The association with obstructive duodenocolic bands and faulty mesenteric fixations (adhesions, kinking, volvulus) should be considered in the context of a proper clinical setting.

A variety of isolated, segmental and intermediary forms of malrotations has been presented, discussed, and illustrated.

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ARTERIOGRAPHY OF RETROPERITONEAL LYMPHOMA*

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ABSTRACT:

Arteriography was performed in 16 patients with various types of lymphoma involving the retroperitoneal space. The location and extent of the mass could be predicted in 15 cases, based upon displacement of major arteries or the kidneys. Most of the studies demonstrated some degree of fine reticular neovascularity and staining within the mass; none showed extreme hypervascularity, coarse or ragged vessels, or pooling of contrast medium during the capillary phase. The differential diagnosis of lesions with this appearance includes metastases, sarcomas, neural tumors, and inflammatory masses. Arteriography may possibly prove to be of value in staging certain patients with lymphoma, although definitive assessment of its role must await further prospective studies.

IN the process of staging patients with lymphoma, roentgenologic studies such as intravenous urography, inferior venacavography and lymphangiography are the principal nonsurgical sources of information regarding possible retroperitoneal involvement.[14] Although arteriography is very useful in evaluating primary retroperitoneal masses of all types,[12,15,16] it has been largely bypassed in patients with known lymphoma where secondary or clinically silent disease is being sought. Consequently, there is a distinct paucity of information available regarding the arteriographic appearance of retroperitoneal lymphoma, with only ten reported cases or illustrations having previously appeared in the radiologic literature.[3,12,13,15–17] The purpose of this paper is to describe the arteriographic findings in 16 patients with various types of lymphoma involving the retroperitoneal space and the root of the mesentery. Lesions originating in organs such as the kidneys, adrenals or pancreas are not included.

MATERIAL

Abdominal aortography and appropriate selective visceral arteriography were performed in 16 patients in whom a tissue diagnosis of lymphoma was ultimately made. There were nine cases of lymphosarcoma, five cases of reticulum cell sarcoma and two cases of Hodgkin's disease. In twelve cases, the initial clinical presentation was that of a primary retroperitoneal mass without peripheral or mediastinal lymph node involvement. Symptoms and signs in these patients included abdominal or flank pain, weight loss and a palpable mass. Intravenous urography, barium studies, or both, generally suggested a retroperitoneal mass, and arteriography was then performed to determine the presence or absence of malignancy, the extent of the lesion, and the size and source of its vascular supply. In the remaining four patients, a tissue diagnosis had been already obtained by biopsy of peripheral lymph node masses prior to arteriography, but all four also had clinical symptoms suggesting retroperitoneal involvement.

ARTERIOGRAPHIC FINDINGS

In 15 of 16 cases, the presence of a retroperitoneal mass was signified by displace-

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ment or stretching of one or more major arteries or displacement of the kidneys. The pattern of displacement was of help in determining the site and extent of the lesion. For example, masses in the root of the mesentery tended to displace the superior mesenteric artery, whereas masses located more posteriorly in the perirenal area displaced the renal arteries, kidneys, or aorta. Other affected vessels included the gonadal, splenic, adrenal, hypogastric, and renal capsular arteries.

Twelve of the 16 cases demonstrated some degree of abnormal vascularity, although none was markedly hypervascular. Four showed moderate hypervascularity while eight were sparsely vascularized. In the remaining four cases, the masses appeared entirely avascular. When seen, the abnormal arteries were almost always fine and reticular in nature. In some cases, a blush or stain within the mass was a prominent finding, indicating a profusion of capillaries and arterioles too small to be individually delineated. The coarse and highly irregular vascularity with pooling seen in hypernephromas and certain types of mesenchymal sarcomas was not present in any of our patients. In two cases, arterial encasement was noted, and in three others

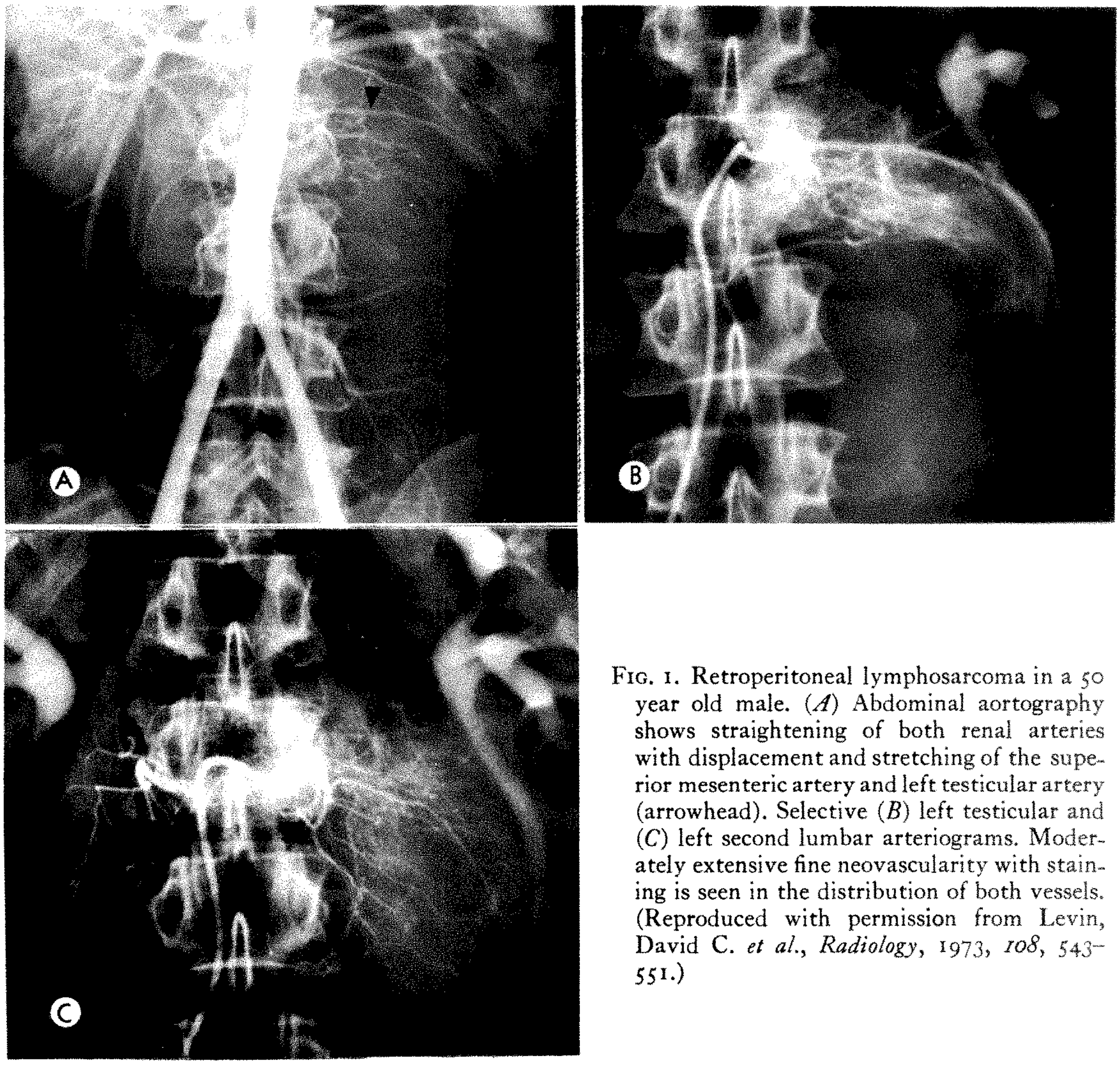

Fig. 1. Retroperitoneal lymphosarcoma in a 50 year old male. (*A*) Abdominal aortography shows straightening of both renal arteries with displacement and stretching of the superior mesenteric artery and left testicular artery (arrowhead). Selective (*B*) left testicular and (*C*) left second lumbar arteriograms. Moderately extensive fine neovascularity with staining is seen in the distribution of both vessels. (Reproduced with permission from Levin, David C. *et al.*, *Radiology*, 1973, *108*, 543–551.)

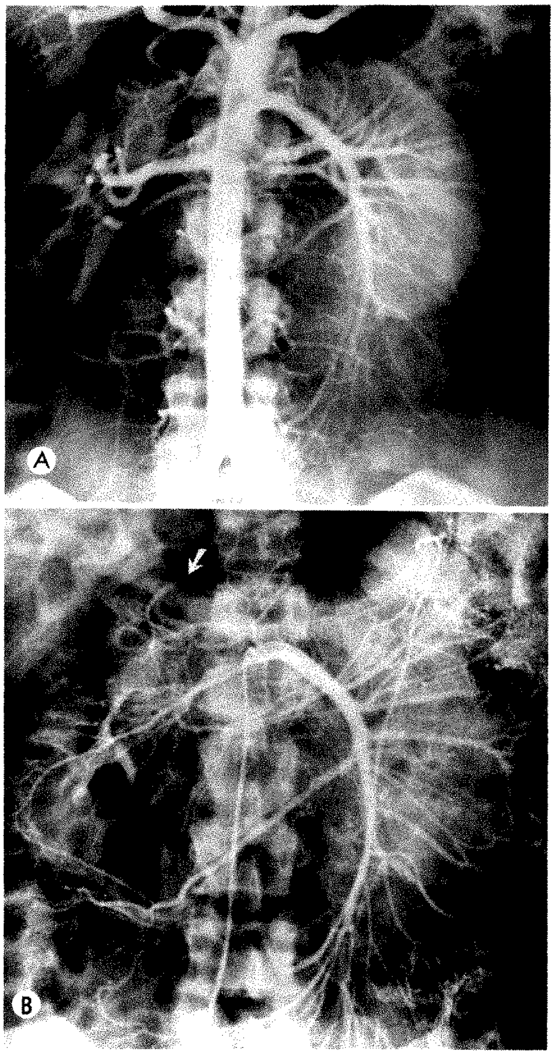

FIG. 2. Retroperitoneal Hodgkin's disease with invasion of the root of the mesentery in a 36 year old female. (*A*) Abdominal aortography shows slight bowing of the aorta to the right and considerable stretching and displacement of the superior mesenteric artery. There is a suggestion of some small abnormal vessels to the left of the aorta. (*B*) Superior mesenteric arteriogram shows stretching of multiple branches. Fine hypervascularity and staining are seen throughout the mesentery with early filling of the portal vein (arrow).

invasion of renal parenchyma was present. In one patient with lymphosarcoma, arteriography was normal, even though lymphangiography and open biopsy revealed retroperitoneal disease.

Figures 1–3 are examples of three moderately hypervascular retroperitoneal lymphomas—two cases of lymphosarcoma and one of Hodgkin's disease. All three show mass displacements of major arteries in the region of the tumor. In each case, selective arteriography of vessels such as the superior mesenteric, gonadal, or lumbar arteries demonstrates fine-caliber neovascularity and staining.

Figures 4-6 are examples of more sparsely vascularized retroperitoneal lymphomas—two cases of lymphosarcoma and one of reticulum cell sarcoma. All three were rather large masses which demonstrated only a few fine abnormal vessels and relatively little staining.

In several cases, the neovascularity did not appear to be homogeneously distributed throughout the tumor mass. That is, abnormal vessels could be seen in one area of the lesion, while other areas appeared to be avascular. The pattern of arterial displacement is therefore a more reliable indicator of size and exact location than the presence of neovascularity in a particular region. The explanation for this lack of homogeneity is not entirely clear.

DISCUSSION

Primary origin of lymphoma within the abdomen is not uncommon, and is estimated to occur in five to ten percent of all patients with this group of diseases.[1,5,18] These cases may be referred for arteriography, especially if the initial evaluation suggests that the mass is located in the retroperitoneal space or root of the mesentery. Our findings indicate that retroperitoneal lymphomas have certain arteriographic features which allow the radiologist to suggest this possibility in his differential diagnosis. These include displacement of major arteries, the presence of fine-caliber neovascularity, and staining generally proportional to the amount of neovascularity. Non-homogeneous distribution of vessels within the mass may be present. Approximately one-quarter of these lesions will be completely avascular. Of the four such patients in our series, two had studies which were performed a number of years ago and were not felt to be of optimal quality.

It is important to be aware that other lesions such as malignant mesenchymal sarcomas, metastases, neural tumors, and inflammatory masses can also produce similar arteriographic changes.[15] Figure 7 demonstrates a neuroblastoma in the retroperitoneal space and transverse mesocolon in an eight year old boy, while Figure 8 is an example of tuberculous mesenteric lymphadenitis in an adult male. Both arteriograms show fine neovascularity with staining and would be difficult to distinguish angiographically from some of our cases.

The findings in this study also suggest at least a potential role for arteriography in the staging of patients in whom the diagnosis of lymphoma has already been estab-

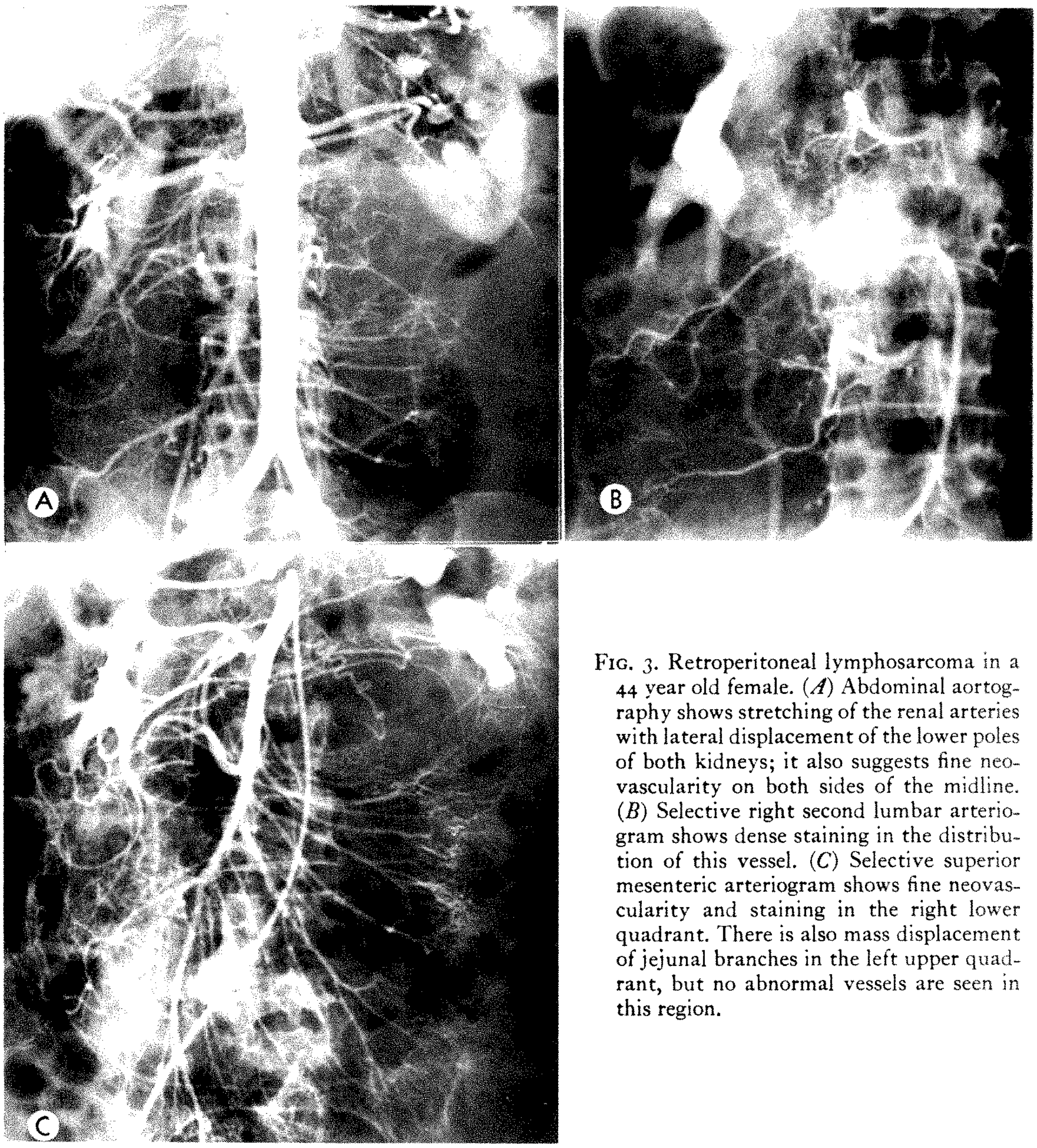

FIG. 3. Retroperitoneal lymphosarcoma in a 44 year old female. (*A*) Abdominal aortography shows stretching of the renal arteries with lateral displacement of the lower poles of both kidneys; it also suggests fine neovascularity on both sides of the midline. (*B*) Selective right second lumbar arteriogram shows dense staining in the distribution of this vessel. (*C*) Selective superior mesenteric arteriogram shows fine neovascularity and staining in the right lower quadrant. There is also mass displacement of jejunal branches in the left upper quadrant, but no abnormal vessels are seen in this region.

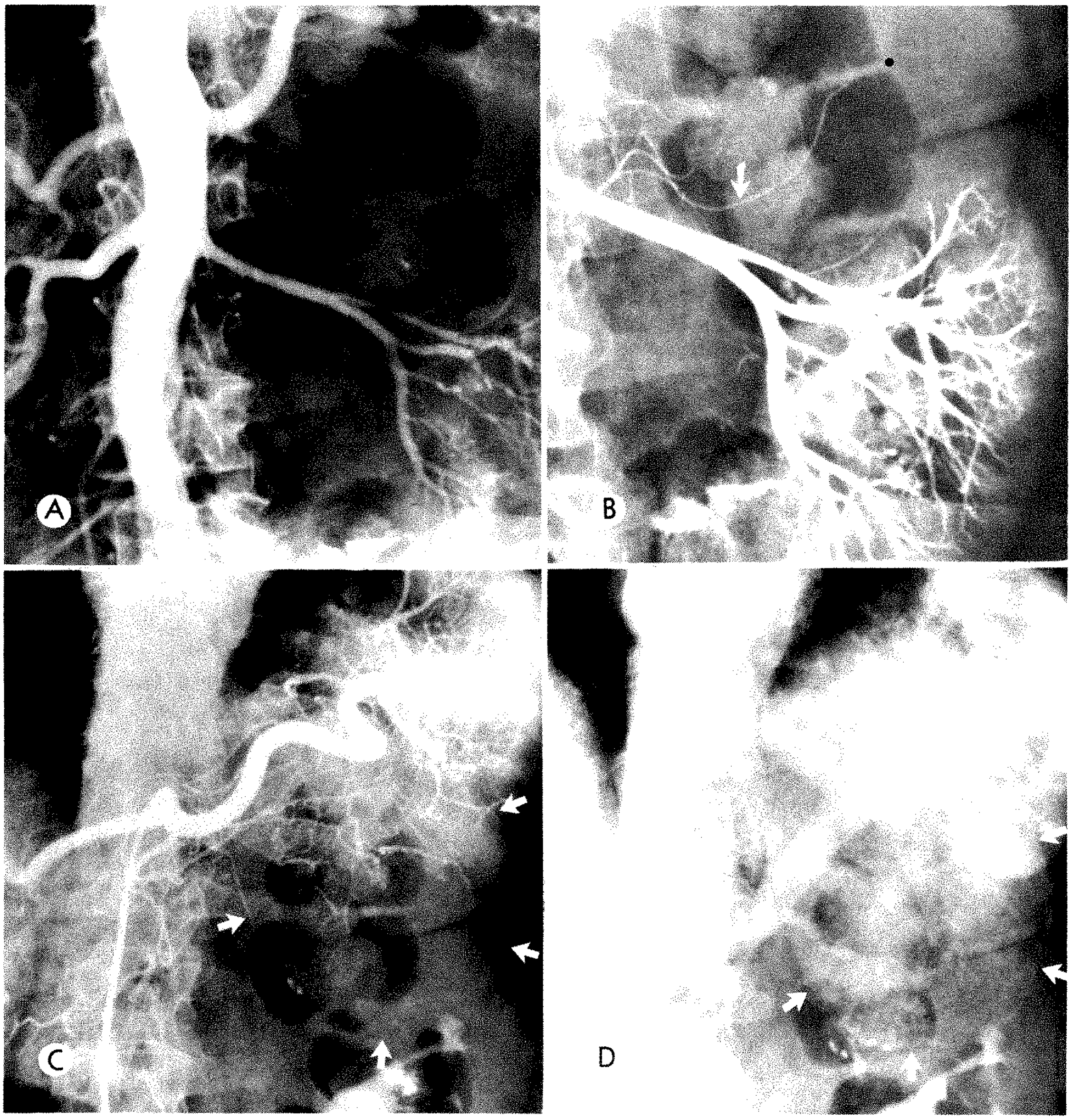

Fig. 4. Reticulum cell sarcoma in the splenic hilar region in a 65 year old female. (*A*) Abdominal aortography shows caudal displacement of the left kidney and stretching of the left renal artery. The splenic artery is elevated. No abnormal vessels are seen. (*B*) A selective left renal arteriogram shows an intrinsically normal left kidney with mass displacement of branches of the left inferior adrenal artery (arrow) but no abnormal vascularity. (*C* and *D*) Arterial and venous phase films from a celiac axis injection. The tumor (outlined by arrows) is supplied by a relatively small number of vessels arising from pancreatic and splenic branches. Some irregularity and encasement of these vessels is present. Faint staining delineates the lesion during the venous phase.

lished by peripheral lymph node biopsy. According to current practice, the principal method of investigation of the retroperitoneal space in these patients is lymphangiography. The heavy emphasis on this technique, however, has been shown to be fraught with pitfalls. Various groups of investigators have compared the results of staging laparotomies with lymphangiography and found significant discrepan-

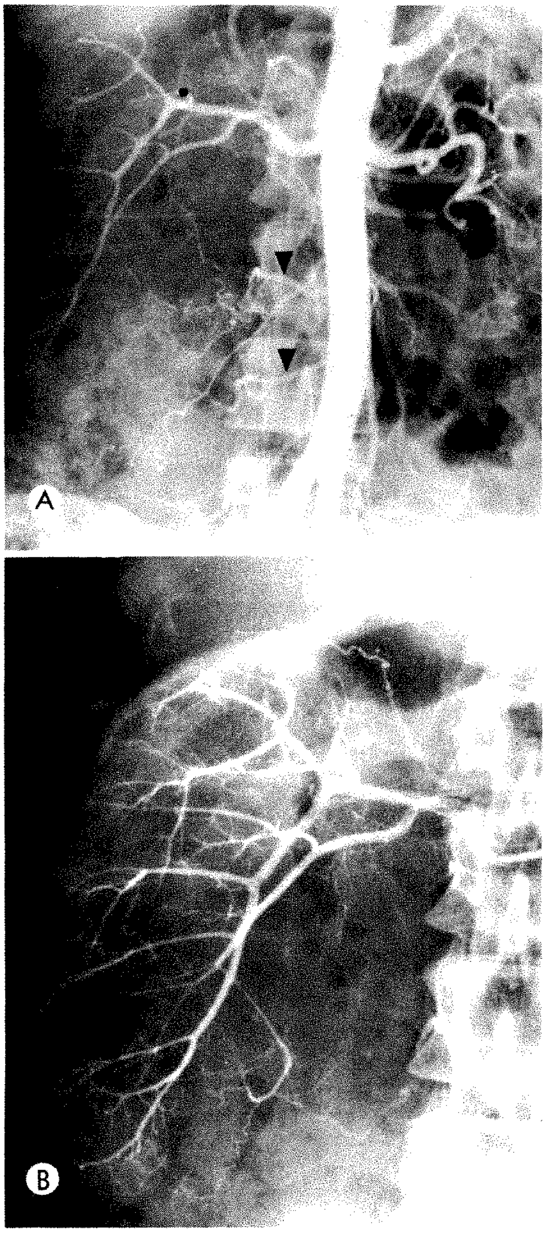

FIG. 5. Right retroperitoneal lymphosarcoma in a 56 year old male. (*A*) Abdominal aortography demonstrates spreading and stretching of the branches of the right renal artery. The distal aorta is bowed slightly to the left. The lower right lumbar arteries (arrowheads) are enlarged and give rise to fine-caliber neovascularity. (*B*) Late phase of a selective right renal arteriogram. Spreading and encasement of segmental and interlobar branches are seen. Abnormal vascularity of a reticular nature is also present throughout the kidney, extending out into the perirenal space medially. Exploration revealed a large tumor mass enveloping the right kidney.

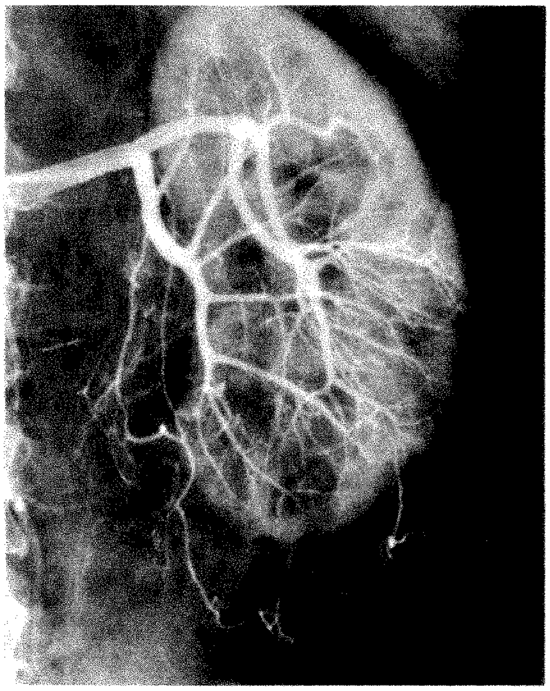

FIG. 6. Lymphosarcoma involving the left perirenal area in a 62 year old male. The lesion is below and medial to the kidney, and most of the fine vessels supplying it arise from ureteral and renal capsular arteries.

cies.[2,4,7,9,11,20] From 10–50 percent of their patients with negative or equivocal lymphangiograms actually had positive lymph nodes at exploration. The reason for the inaccuracy appears to be that several important groups of lymph nodes are not opacified by standard pedal lymphangiography. These include lymph nodes in the porta hepatis and splenic hilum, and in the mesenteric, celiac, and upper periaortic areas. Goffinet *et al.*[8] found, for example, that fully 61 percent of patients with non-Hodgkin's lymphoma who underwent staging laparotomies had mesenteric lymph node disease; none of this had been detected by lymphangiography.

The increasing use of diagnostic laparotomy and splenectomy has improved the accuracy of staging of Hodgkin's disease in a number of academic centers. This policy has not been universally accepted at all hospitals, however, and it has been employed in even more limited fashion in non-

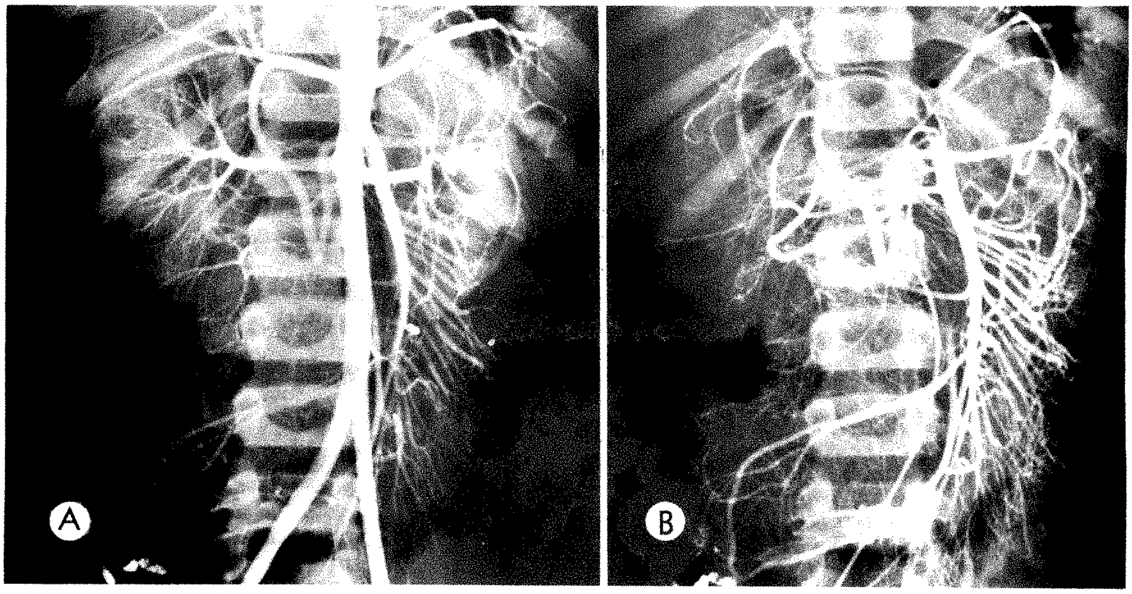

FIG. 7. Neuroblastoma of the transverse mesocolon and retroperitoneal space in an eight year old male. (*A*) Aortography reveals straightening of the right renal artery and bowing of the aorta and superior mesenteric artery to the left. (*B*) Superior mesenteric arteriography shows diffuse fine neovascularity with spreading and stretching of colic branches.

Hodgkin's lymphoma.[8,10,21] Surgical exploration itself is not without its pitfalls. It may be difficult for the surgeon to inspect carefully all lymph node-bearing areas within the abdomen, and there is reason to believe that a significant number of positive lymph nodes escape discovery.[7,10,19] Furthermore, from 8–22 percent of these procedures have been associated with significant postoperative complications.[6,8,19] Fi-

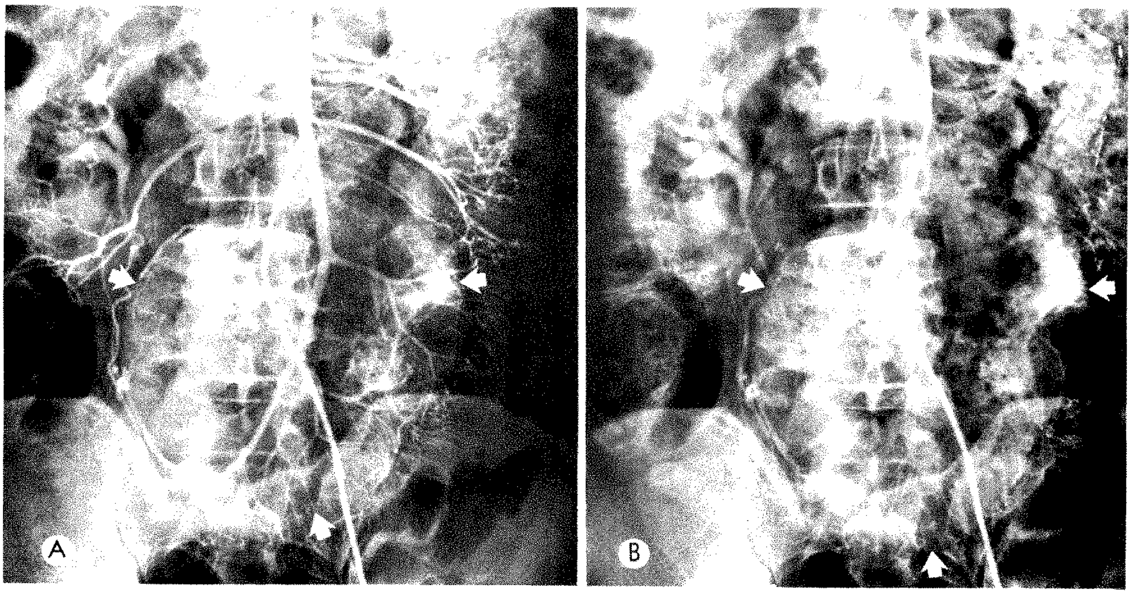

FIG. 8. Tuberculous mesenteric lymphadenitis in a 24 year old male. (*A* and *B*) Arterial and capillary phases of a superior mesenteric arteriogram show a moderately vascular mass (arrows) in the mesentery. The vessels supplying the mass are of small caliber. Non-homogeneous staining is seen during the capillary phase.

nally, patient acceptance of non-therapeutic major surgery may be limited. These shortcomings emphasize the continued importance of an aggressive roentgenologic approach to evaluation of the retroperitoneal space in patients with known lymphoma. Arteriography has not been put to such use on an extended prospective basis and there are thus no data as yet regarding its efficacy. We feel it may conceivably add valuable information, particularly in cases of symptomatic non-Hodgkin's lymphoma where lymphangiography is negative or equivocal and where exploratory surgery is not contemplated.

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ROENTGENOLOGY-PATHOLOGY CORRELATIVE STUDY OF NEOVASCULARITY*

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ABSTRACT:

In an attempt to evaluate the histologic picture of what is shown on angiograms as neovascularity, several benign and malignant tumors were examined. New vessels (neovascularity) are large capillaries or sinusoids, and neither contain smooth muscle in their walls. The walls may contain some fibrous connective tissue. Puddling, laking, and staining represent the collection of contrast medium in small capillaries or sinusoids. Some tumors, such as hemangioma of the liver, cystadenoma of the pancreas, and angiomyolipoma of the kidney contained abnormal vascularity, but this was not composed of vessels which had arisen or developed anew, as there was smooth muscle in their walls, and this indicates that those vessels had been there from birth. In xanthogranulomatous pyelonephritis and chronic renal disease, the appearance of increased vascularity is the result of rearrangement of the normal vascular structures.

SINCE radiologists began evaluating tumors, inflammations, arteriovenous malformations and other abnormalities angiographically, the vascular patterns of these lesions have indeed been fascinating subjects. A variety of excellent papers has been published describing these various angiographic patterns. Terms such as neovascularity, puddling, laking, staining, and early venous filling have been ubiquitous in the vocabulary of the angiographer, and have been associated with tumors, both malignant and benign.

Some confusion seems to exist, however, as to the exact nature of the meaning of these terms from a pathologic standpoint. Exactly what constitutes "neovascularity"? Can the neovascularity that has been associated with tumors be differentiated both angiographically and pathologically from the vascularity that has been associated with inflammatory disease? We shall attempt to clarify exactly what neovascularity, puddling, staining and other associated terms mean.

MATERIAL AND METHOD

We evaluated the angiograms of 13 cases of xanthogranulomatous pyelonephritis, 14 tumors both benign and malignant, and two cases of chronic renal disease (Table 1) with emphasis on the vascular patterns. We then studied the vascular patterns of these cases microscopically utilizing Masson's trichrome stain in each case to differentiate between smooth muscle and fibrous connective tissue in the walls of blood vessels within the tumors and inflammations. We also stained each tissue section with Van Gieson's elastic stain in order to identify the internal elastic lamellae of arteries in order to differentiate arteries from veins.

RESULTS

Smooth muscle neither regenerates nor proliferates to any significant degree. If normal smooth muscle can be found in the walls of arteries with a normal architecture, then one may assume that that artery is not new; *i.e.*, it does not represent neo-

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Table I

Diagnosis	Angiographic Pattern	Pathology of Vessels	Comments
1. Chronic renal disease	Tortuous arteries	Normal arteries with hypertrophic media, large veins	Some arterial lumens sealed with fibrous connective tissue
2. Chronic renal disease	Tortuous arteries	Normal arteries with hypertrophic walls, large veins	
3. Xanthogranulomatous pyelonephritis (13 cases)	Some avascular, others with arterial vascularity	Many arteries with hypertrophic musculature in walls but no large capillaries	
4. Wilms' tumors (2 cases)	Neovascularity	Predominantly large capillary-like vessels with few sinusoids	
5. Renal cell carcinoma metastatic to bone	Neovascularity	Large capillary-like vessels	
6. Leiomyosarcoma metastatic to liver	Neovascularity and puddling	Large capillary-like vessels and multiple small sinusoids	Fibrous connective tissue in walls, disorganized
7. Hepatoblastoma	Neovascularity	Large capillary-like vessels some with well organized fibrous connective tissue surrounding them, some sinusoids	Fibrous connective tissue in walls, well organized in some vessels, others no connective tissue
8. Benign neuroendocrine tumor; carcinoid islet cell histologic type,[15] secreting insulin	Arteries on periphery of tumor, staining in tumor	Myriads of sinusoids, and capillaries, occasional vein	
9. Malignant neuroendocrine tumor, carcinoid islet cell histologic type, secreting insulin	Neovascularity? Staining	Large capillaries, some sinusoids, no arteries, occasional vein that may have been engulfed by tumor	"Angrier" looking than benign tumor
10. Benign neuroendocrine tumor, pheochromocytoma. Histologic type secreting catecholamines	Staining	Large capillaries and sinusoids, some veins, myriads of small capillaries and sinusoids	
11. Benign neuroendocrine tumor, pheochromocytoma histologic type, secreting catecholamines	Neovascularity, minimal staining	Large capillaries with fibrous connective tissue in walls	
12. Hemangioma	Puddling	Large channels, walls mostly normal looking smooth muscle; congenital	Small amounts of connective tissue in smooth muscle indicating growth. Others have described walls comprised of connective tissue
13. Cystadenoma pancreas	Tortuous arteries; no staining	Normal arteries and veins in capsule. Tiny capillaries in adenomatous part	
14. Angiomyolipoma kidney	Abnormal vascularity	Many huge arteries, smaller arterioles, veins	Abnormal vascularity but not neovascularity

vascularity. Upon microscopic examination of numerous pathologic sections from patients with xanthogranulomatous pyelonephritis (XP), we found numerous arteries of normal architecture with normal smooth muscle in their walls. However, microscopic examination of patients with renal cell carcinomas revealed essentially no arteries of normal architecture with smooth muscle within tumor parenchyma. Rather, the predominant blood vessels within these tumors were large endothelial lined vessels with perhaps some fibrous connective tissue surrounding them. We found none of these

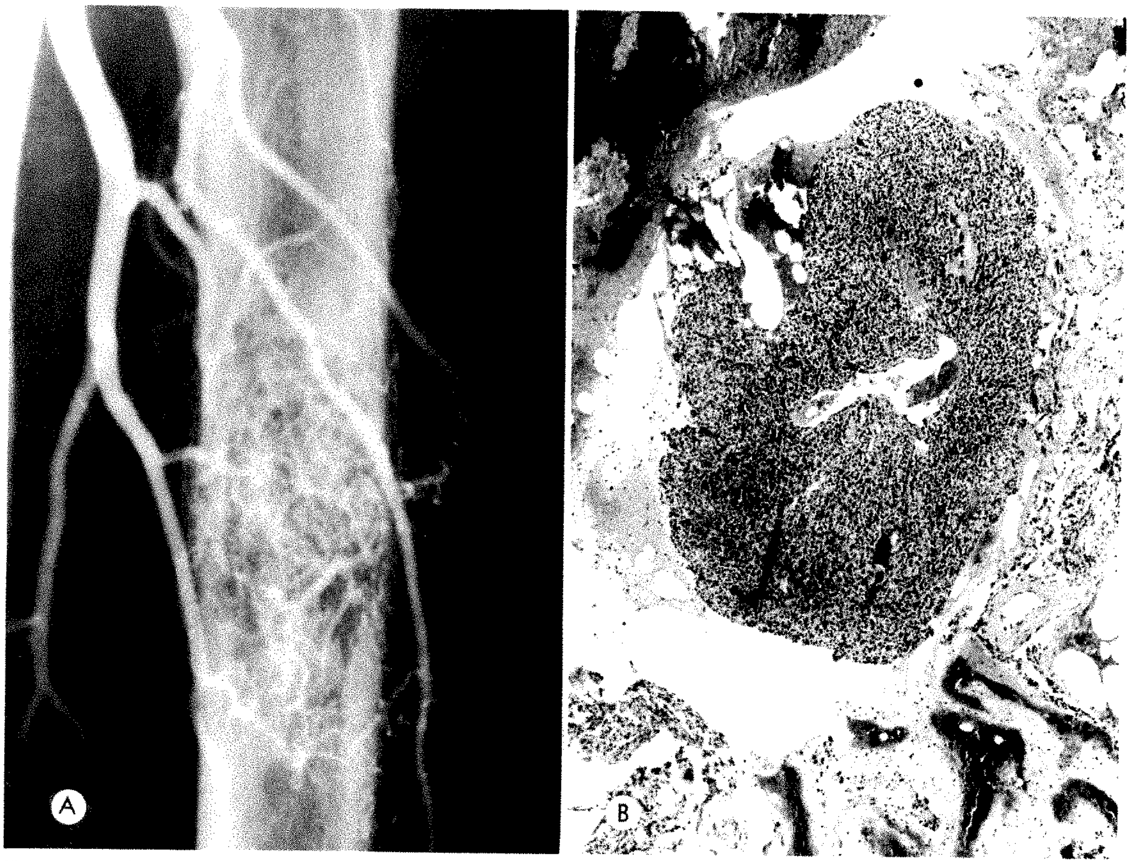

FIG. 1. (*A*) Metastatic renal cell carcinoma to bone. Note neovascularity. (*B*) Microscopic specimen shows large capillary in center of metastatic deposit surrounded by smaller capillaries.

large capillary-like vessels in the tissue sections from patients with XP. We concluded from these observations that new vessels (neovascularity) associated with renal carcinomas were not arteries but were actually huge capillary-like vessels with or without fibrous connective tissue surrounding them and that XP produced no neovascularity because the predominant blood vessels within these inflammations were arteries of normal architecture.

The results of microscopic examination of 13 other tumors and two cases of chronic renal disease are summarized in Table 1. In most tumors, large arteries with normal architecture could be observed along their margins. However, within the parenchyma of both the benign and malignant tumors, we could find no arteries with normal architecture. Rather, the predominant vessels were either large and small sinusoids (*i.e.*, channels with no endothelial lining) or both small and large vessels with endothelial lining presenting the same appearance as the blood vessels that we observed in the renal cell carcinomas (Fig. 1–4). An occasional vein could be found within the parenchyma of several of the tumors. These veins were possibly engulfed by the growing tumors.

The predominant vessels within the parenchyma of the angiomyolipoma were large arteries and veins and smaller arterioles and venules with normal architecture (Fig. 7). We therefore believe that the majority of the blood vessels that could be seen on the arteriogram of the angiomyolipoma were arteries and veins (*i.e.*, because of their size and number). Thus the vascularity that we observed in this tumor was not neovascularity.

The angiographic pattern of the cystadenoma of the pancreas showed some tortuous vessels overlying the tumor. Microscopic examination showed normal arteries and veins in the capsule of this tumor (Fig. 6). Examination of the adenomatous part of this tumor showed only tiny capillaries. However, this tumor did not stain angiographically. The majority of cystadenomas that have been reported in the literature stained on angiograms.[1,8,10] The pathologic changes producing this angiographic staining are not known.

Large arteries and veins with hypertrophic walls surrounded the periphery of the multiple hemangiomas of the liver that we studied. The hemangiomas themselves were composed of large irregular vascular channels with normal appearing smooth muscle within the walls. A small amount of fibrous connective tissue was mixed in with the smooth muscle. This normal appearing smooth muscle would suggest that these hemangiomas are congenital but have grown and that the growth stimulated some fibrous connective tissue among the smooth muscle. Others have reported that the predominant tissue in the walls of hemangiomas of the liver is fibrous connective tissue.[9]

The patients with non-specific chronic renal disease showed tortuous arteries on the arteriograms, numerous arteries of normal architecture with hypertrophic musculature in the walls pathologically, and no large sinusoids nor capillary-like vessels.

DISCUSSION

There has been little specific discussion of the pathologic nature of neovascularity and related vascularity. Several terms have been used to describe the vascularity associated with tumors. These include neovascularity, tumor vascularity, and malignant neovascularity.[2,8,11,14] Terms used to describe the vascularity associated with inflammatory disease include benign neovascularity, hypervascularity, and discrete hypervascularity-none of these terms has been related to pathologic findings.

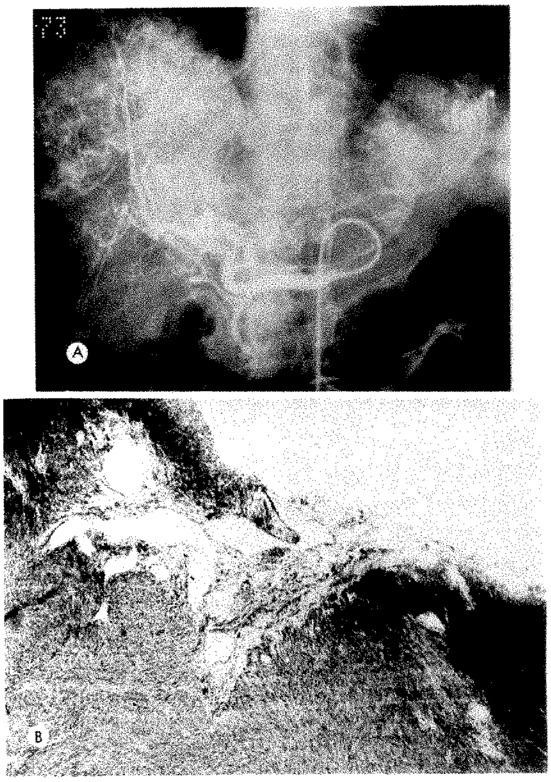

FIG. 2. (*A*) Metastatic leiomyosarcoma to liver. Note neovascularity, puddling, and tumor stain on angiogram. (*B*) Microscopic section shows capillaries surrounded by fibrous connective tissue in upper part of photograph and slit-like sinusoids in lower part.

From the angiographic standpoint, neovascularity has usually been thought of as blood vessels that are more tortuous than normal vessels, that are purposeless in direction and that do not taper toward the periphery of the organ in which they are found, but rather narrow and widen in a haphazard fashion. Neovascularity has been described in association with not only malignant and benign tumors but with certain inflammatory conditions.[3,4,13,15] It became apparent upon evaluating the angiograms of several patients with XP that although the blood vessels in these lesions were purposeless in direction and extremely tortuous, in general they tapered more than the neovascularity associated with renal cell carcinomas. This observation has also been made by other authors.[3,15] These vessels have been called "benign neovascularity." In a previously published paper, we showed pathologically that the vessels associated with xanthogranulomatous pyelonephritis were apparently all arteries with histologically normal architecture and therefore not neovascular.[7]

Since sinusoids and endothelial lined vessels without muscular walls are essentially the only vessels present within the parenchyma of the tumors we examined, we assume that neovascularity is made up of huge sinusoids and capillaries that may or may not be surrounded by fibrous connective tissue. Three possibilities seem to exist as to the origin of these capillaries. One is that normal existing capillaries dilate in response to tumor growth. The second is that new capillaries proliferate in response to tumor growth, and the third is that a combination of these two phenomena occurs. It seems plausible that since both in normal organs and in tumors, arteries supply capillaries which then drain into veins, at least a portion of the development of neovascularity is the result of the enlargement of existing capillaries. Because tumor growth has been reputed to stimulate capillary growth,[14] some new capillaries probably develop in response to the tumor. Since the sinusoids are not lined with endothelium, we assume that they are simply holes in tumor parenchyma that transfer blood from arteries extrinsic to the tumor to capillaries or veins supplying blood to the tumor as they course through it. Why they develop is not clear.

Tumors that stained angiographically but contained very little if any neovascu-

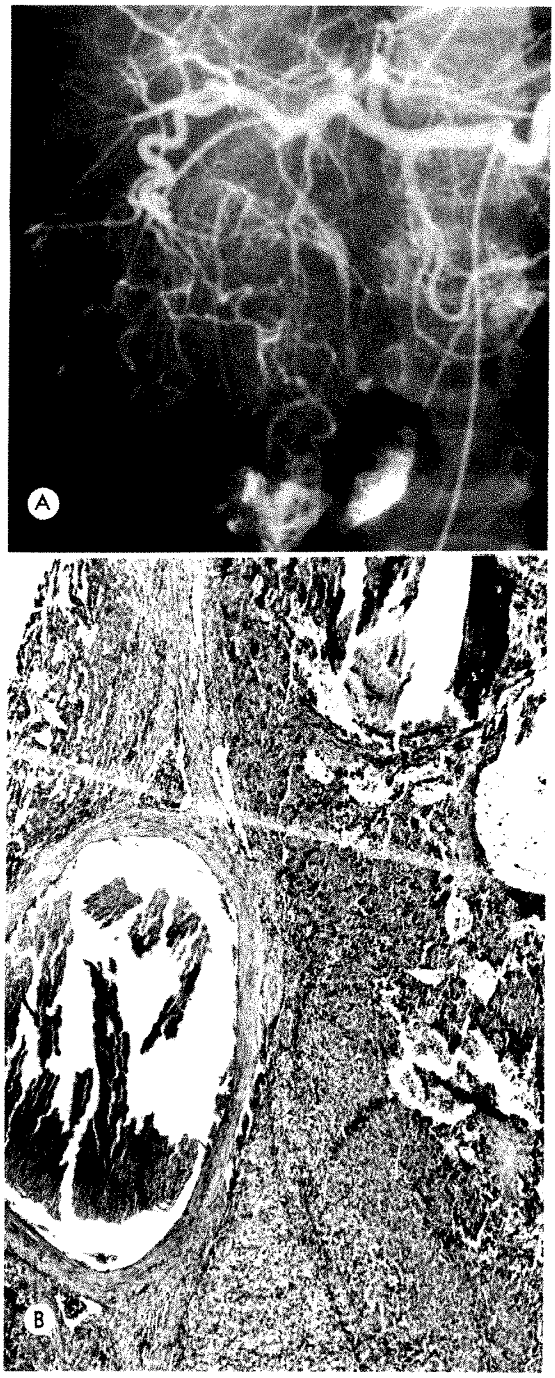

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FIG. 3. (*A*) Hepatoma. Extensive neovascularity along inferior margin of liver being fed by several large arteries extrinsic to the tumor. (*B*) Microscopic section shows a large capillary surrounded by fibrous connective tissue (proved by trichrome stain) on left hand side of photograph. Note smaller capillaries and sinusoids on right. Prominent arteries were identifiable in the capsule of the tumor but none was present within the parenchyma of the tumor.

larity angiographically showed myriads of small capillary-sinusoid-like vessels or extremely large sinusoids on microscopic examination (Fig. 4; and 5). This would suggest that neovascularity and tumor staining are different expressions of the same phenomenon along a continuum. Because the vessels within the hemangioma contained normal smooth muscle, we assume that the angiographic staining within this tumor is based on a different pathological phenomenon than in the other tumors that we examined. Apparently the vasculature associated with the hemangioma is, at least in part, congenital. The blood vessels that we observed angiographically and pathologically in the cystadenoma of the pancreas were arteries and veins and therefore not new vessels. However, this tumor showed only minimal vascularity and no staining angiographically. Since only arteries and veins were present within the angiomyolipoma that we studied, we question whether these tumors develop neovascularity. Rather, what we observed angiographically is apparently abnormal vascularity that is congenital in origin.

Viamonte *et al.*[14] discussed the nonspecificity of abnormal vascularity in the angiographic diagnosis of malignant neoplasms. They commented that tumor cells appear to stimulate endothelial cell proliferation, and that endothelial cells may have an indirect effect on the rate of tumor growth. They described the following changes associated with tumors: abnormality of distal arteries; lack of normal continuous tapering; polymorphism (ectatic, irregular branches larger than parent vessel); abnormal course and distribution; obstruction;

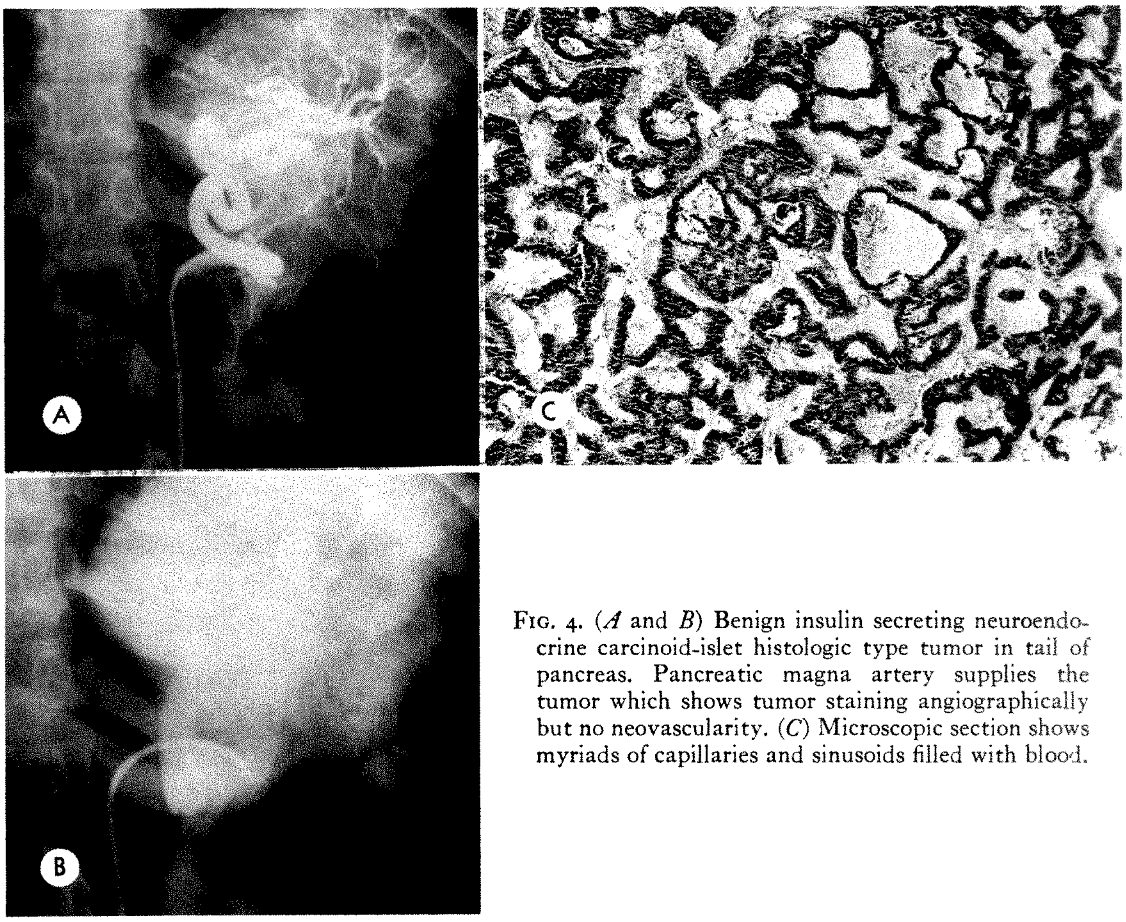

Fig. 4. (*A* and *B*) Benign insulin secreting neuroendocrine carcinoid-islet histologic type tumor in tail of pancreas. Pancreatic magna artery supplies the tumor which shows tumor staining angiographically but no neovascularity. (*C*) Microscopic section shows myriads of capillaries and sinusoids filled with blood.

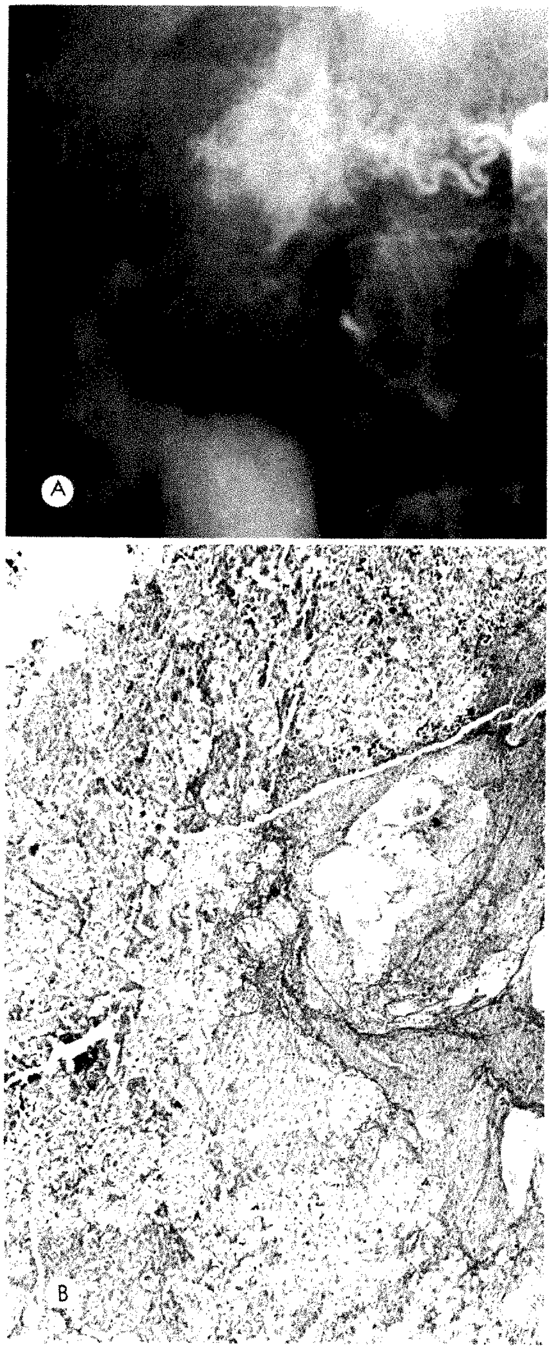

FIG. 5. (*A*) Benign neuroendocrine tumor pheochromocytoma histologic type secreting catecholamines along sympathetic chain supplied by large, tortuous lumbar artery. No vascularity is visible but the tumor stains intensely angiographically. (*B*) Microscopic section shows myriads of capillaries and sinusoids. Vessels in the right side of the photograph are surrounded by fibrous connective tissue.

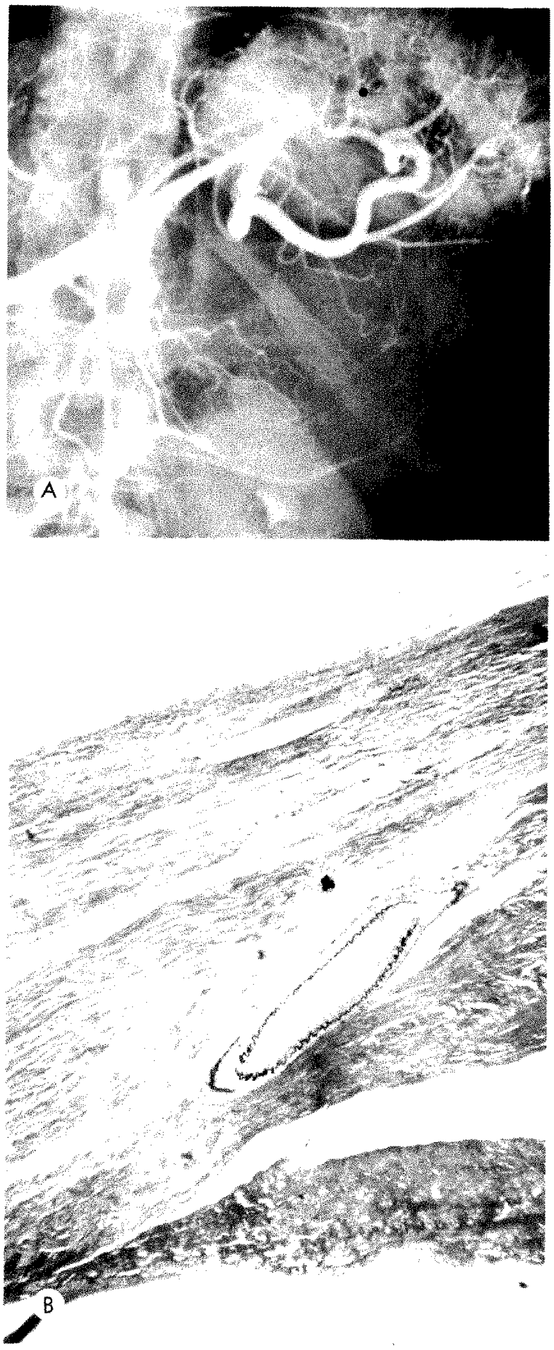

FIG. 6. (*A*) Cystadenoma of pancreas. Angiogram shows prominent, tortuous vessels supplying the tumor but no tumor staining angiographically. (*B*) Microscopic section of capsule of tumor. Note normal artery with black staining internal elastic lamella in center of picture and vein superior to it. No capillaries present in capsule. The vessels seen angiographically were not neovascularity (*i.e.*, they were arteries).

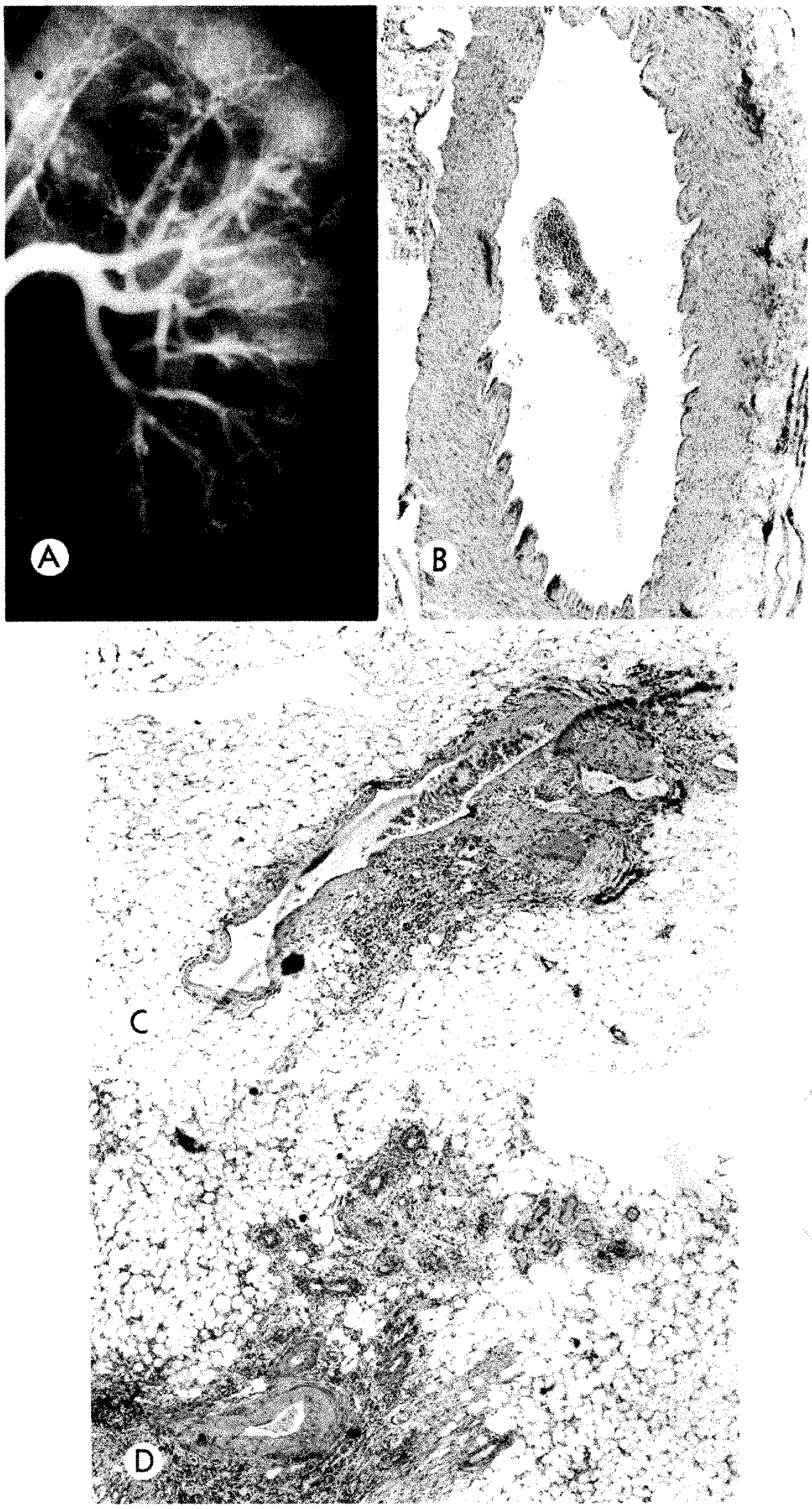

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Fig. 7. (*A*) Angiomyolipoma of kidney shows abnormal vascularity in upper pole of kidney. Microscopic sections show (*B*) large arteries (*C*) large veins with medium sized arteries and (*D*) arterioles and venules but no large capillaries as were observed in other tumors.

tumor "sinusoid" formation; and arteriovenous shunting.

We emphasize that we observed no arteries within the parenchyma of the tumors that we examined except for the angiomyolipoma (Table 1). There were prominent arteries around the periphery of many of the tumors outside the capsules (when present) and within normal parenchyma of the organs involved.

From our observations (Table 1) it seems that both the angiographic and pathologic patterns of the benign and malignant tumors (except for angiomyolipoma and hemangioma) were too similar to confidently differentiate, although the vascularity of the malignant, insulin secreting neuroendocrine tumor did show an "angrier" appearance microscopically than the benign tumor that secreted insulin.

In this retrospective study we were unable to perform roentgenography of pathologic specimens of tumors after injecting them with contrast material, marking the blood vessels of these pathologic specimens, and sectioning the blood vessels to compare directly to those seen angiographically. This procedure would offer more direct information.

CONCLUSIONS

Since normal smooth muscle essentially neither proliferates nor regenerates, if the wall of a blood vessel contains normal smooth muscle and the blood vessel is of normal architecture, then it is not a new vessel (*i.e.*, does not represent neovascularity). According to observations made on multiple pathologic sections of several benign and malignant tumors, new vessels (neovascularity) are actually large capillaries or sinusoids with no smooth muscle in the walls. The walls of these vessels may contain some fibrous connective tissue.

Puddling, laking, and staining represent the collection of contrast material in myriads of small capillaries or sinusoids, or both.

Inflammatory conditions such as xanthogranulomatous pyelonephritis and chronic renal disease develop no neovascularity but appear to show increased vasculature because of rearrangement of normal vascularity.

Certain tumors contained abnormal vascularity which, at least in part, was not neovascularity because the walls of the blood vessels in these lesions contained normal smooth muscle. These tumors include a hemangioma of the liver, a cystadenoma of the pancreas, and an angiomyolipoma of the kidney. Further study is needed to elucidate this.

No definite histological criteria seem to exist that would allow differentiation between the vascularity associated with benign and malignant tumors.

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COMPLICATIONS OF PERCUTANEOUS TRANSAXILLARY CATHETERIZATION FOR ARTERIOGRAPHY AND SELECTIVE CHEMOTHERAPY*

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ABSTRACT:

This report enumerates and analyzes the complications of percutaneous transaxillary catheterization encountered in 200 consecutive patients undergoing diagnostic arteriography, and 20 consecutive patients who had catheter placement for selective chemotherapy. Diagnostic arteriography led to minor complications in eleven percent and major complications in two percent. Risk correlated with the type of procedure, number of catheter exchanges and particularly, the presence of arteriographic risk factors, such as hypertension, bleeding tendencies, and advanced atherosclerosis. Therapeutic catheter placements had a 15 percent incidence of minor and a 20 percent incidence of major complications. Here, also, complications were more likely in the presence of the arteriographic risk factors. Suggested means for decreasing the hazards of the transaxillary catheterization include: exclusion of high risk patients, use of a proper puncture site, careful catheter manipulation, the fewest possible catheter exchanges, correct manual hemostasis following catheter withdrawal, and close observation of the patient after the procedure. Early surgical intervention is indicated in the presence of a progressively developing neural defect.

VARIOUS complications have been reported with percutaneous axillary catheterization for diagnostic arteriography and selective chemotherapy. Following diagnostic arteriography, these have ranged from minor hematoma and transient spasm to arterial occlusion, brachial plexus injury, and cerebral accident.[2–5,8–10,12,13,15,16,18] Use of the axillary route for selective chemotherapy has been complicated by local infection, loss of radial pulse, septic embolization and cerebral accident.[6,19] Although the foregoing catheterizations involve the same artery, different circumstances warrant their separate risk assessment. This report reflects our belief that an objective assessment of the risks of the axillary route can place it in proper perspective with the femoral route and indicate useful preventive measures.

In performing over 8,000 arterial catheterizations during the last six years, we have used the percutaneous axillary route as an alternate or complement to the femoral over 500 times. Most procedures were done by trainees under staff supervision. We have identified and reviewed the complications encountered in 200 consecutive patients who had transaxillary arteriograms during 1972 and 1973 and in 20 consecutive patients who had selective chemotherapy *via* the same route from 1969 to 1973. We have analyzed the frequency of complications in relation to procedure type, catheter size, number of catheter exchanges, and the presence of arteriographic risk factors such as bleeding tendencies, hypertension, atherosclerosis, and duration of chemotherapy. On the basis of our findings and the reports of other authors, means for prevention of complications have been suggested.

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Table I

INCIDENCE OF COMPLICATIONS IN RELATION TO THE TYPE OF PROCEDURES IN 200 PATIENTS WITH DIAGNOSTIC TRANSAXILLARY ARTERIOGRAMS; STATISTICAL EVALUATION: 1 *vs* 2—$P<.025$, 1 *vs* 3—$P<.05$, 1 *vs* 4—$P>.5$

Type of Angiographic Procedures	No. of Patients	Minor Complications (11 percent)				Major Complications (2 percent)			
		Temporary Spasm		Insignificant Hematoma		Hematoma with Consequences		Cerebral Accident	
		No.	Percent	No.	Percent	No.	Percent	No.	Percent
1. Aortofemoral	139	3	2	6	4	2	1.5	—	—
2. Coronary	25	1	4	5	20	—	—	1	4
3. Thoracic aortogram, brachiocephalic studies	21	1	5	4	19	—	—	1	5
4. Visceral	15	—	—	2	13	—	—	—	—
Total	200	5	2.5	17	8.5	2	1	2	1

MATERIAL AND METHOD

Of the 200 patients who underwent diagnostic transaxillary catheterization, 137 were male and 63 female, ranging in age from 37 to 79 years (mean 64). Obstructive pelvic atherosclerotic disease with absent femoral pulses, inability to pass the catheter into the aorta or control the catheter for selective catheterization were our indications for use of the axillary approach. The types of studies performed are listed in Table I. Aortofemoral, coronary and visceral arteriograms were done *via* the left axillary artery; thoracic aortograms and brachiocephalic arteriograms, *via* the right. Catheter sizes ranged from 5.4 to 7 French (Table II). Most studies were done with one catheter; one or more catheter exchanges were necessary in about 25 percent (Table III). Bleeding tendencies (coagulation studies below 50 percent of normal, evaluation by prothrombin time or the activated partial thromboplastin time, or both), systemic hypertension (over 170/100 mm Hg), and atherosclerotic disease of the aortic arch (evidenced by prominence and calcification on chest roentgenograms) were considered to be risk factors for the percutaneous axillary catheterization (Table IV).

Of the 20 patients who had selective

Table II

INCIDENCE OF COMPLICATIONS IN RELATION TO THE SIZE OF THE CATHETERS USED IN 200 PATIENTS WITH DIAGNOSTIC TRANSAXILLARY ARTERIOGRAMS; STATISTICAL EVALUATION: 1 *vs* 2—$P>.9$, 1 *vs* 3—$P>.9$

Size of Catheter	Type of Angiographic Procedures	No. of Patients	Minor Complications (11 percent)				Major Complications (2 percent)			
			Temporary Spasm		Insignificant Hematoma		Hematoma with Consequences		Cerebral Accident	
			No.	Percent	No.	Percent	No.	Percent	No.	Percent
1. 5.4 Fr	Brachiocephalic	6	—	—	1	17	—	—	—	—
2. 6.6 Fr	Thoracic, brachiocephalic, aortofemoral, visceral	169	4	2.4	11	6.5	2	1.2	1	0.6
3. 7 Fr	Coronary	25	1	4	5	20	—	—	1	4

TABLE III

INCIDENCE OF COMPLICATIONS IN RELATION TO THE CATHETER EXCHANGES IN 200 PATIENTS WITH DIAGNOSTIC TRANSAXILLARY ARTERIOGRAMS; STATISTICAL EVALUATION: 1 *vs* 2—$p<.025$, 1 *vs* 3—$p<.005$

Number of Catheter Exchanges	No. of Patients	Minor Complications (11 percent)				Major Complications (2 percent)			
		Temporary Spasm		Insignificant Hematoma		Hematoma with Consequences		Cerebral Accident	
		No.	Percent	No.	Percent	No.	Percent	No.	Percent
0	142	1	0.7	7	5	1	0.7	1	0.7
1	27	2	7	4	15	1	3.7	1	—
2 or more	31	2	6	6	19	—	—	1	3

chemotherapy *via* an axillary catheter, 13 were female and seven male, ranging in age from 35 to 68 years (mean 49). Either the presence of iliofemoral occlusive disease or the need to give long-term infusions to ambulatory patients governed our choice of the axillary route. In twelve patients, the catheter was placed into the hepatic artery for selective infusion therapy of metastatic liver disease by 5-Fluorouracil. Five patients had selective streptokinase treatment for acute occlusion of iliofemoral arteries. The left axillary artery was used in the foregoing 17 cases. In three others, the catheter was introduced *via* the right axillary artery into the external carotid artery for bleomycin infusion therapy of face malignancies. In all 20 cases, 6.6 French polyethylene catheters were utilized. Infusions lasted from one day to one year (mean 48 days) (Table V). For their possible bearing on the complications of indwelling axillary catheters, we assessed the role of age, general atherosclerosis, hypertension, bleeding tendencies, and the type of infused drugs (Table VI).

Complications in both the diagnostic and therapeutic groups were divided into minor (healing spontaneously, no lasting clinical consequences) and major (requiring therapy, usually surgery, or resulting in permanent damage). Minor complications included small local hematomas without consequences and transient spasm of the axil-

TABLE IV

INCIDENCE OF COMPLICATIONS IN RELATION TO THE ARTERIOGRAPHIC RISK FACTORS IN 200 PATIENTS WITH DIAGNOSTIC TRANSAXILLARY ARTERIOGRAMS; STATISTICAL EVALUATION: 1 *vs* 4—$p>.5$, 1 *vs* 5—$p<.01$

Risk Factors	No. of Patients	Minor Complications (11 percent)				Major Complications (2 percent)			
		Temporary Spasm		Insignificant Hematoma		Hematoma with Consequences		Cerebral Accident	
		No.	Percent	No.	Percent	No.	Percent	No.	Percent
1. No risk factors	65	1	1.5	1	1.5	—	—	—	—
2. Bleeding tendency	4	—	—	2	50	—	—	—	—
3. Hypertension	3	—	—	1	33	—	—	—	—
4. Arch atherosclerosis	71	2	3	3	4	—	—	1	1.4
5. Combination of risk factors	57	2	3.5	10	17.5	2	3.5	1	1.8

Table V

INCIDENCE OF COMPLICATIONS IN RELATION TO THE DURATION OF THE INDWELLING CATHETER IN 20 PATIENTS WITH SELECTIVE CHEMOTHERAPY BY THE TRANSAXILLARY ROUTE

Duration of Indwelling Catheter	No. of Patients	Minor Complications (15 percent)		Major Complications (20 percent)	
		Temporary Spasm No.	Insignificant Hematoma No.	Axillary Artery Occlusion No.	Cerebral Accident No.
1–3 days	3	—	—	1	1
3–14 days	7	1	2	1	—
2–4 weeks	5	—	—	—	—
1–6 months	3	—	—	1	—
6–12 months	2	—	—	—	—

lary or brachial artery with temporary decrease or loss of radial pulse. Major complications included local hematoma with consequences, thrombosis of the axillary or brachial artery, brachial plexus damage and cerebral complications; *i.e.*, seizure or stroke. Data were statistically analyzed, using x^2 and unpaired *t*-tests.

RESULTS

In the group of 200 patients who had diagnostic transaxillary catheterization, 22 minor complications (eleven percent) and four major complications (two percent) were encountered. Temporary spasm of the axillary or brachial artery occurred in five patients, and insignificant hematoma in 17. Major complications included two cerebral accidents and two major hematomas which required surgical therapy. Of the former, one patient had a cerebral seizure during brachiocephalic arteriography, but recovered completely. The other, a patient with severe aortic stenosis and advanced atherosclerotic disease, suffered a stroke during difficult, prolonged transaxillary coronary arteriography and died three days later. The two patients with major hematomas had the following courses:

Case i. A 75 year old man with generalized atherosclerosis, a large abdominal aneurysm, and occlusive disease of the pelvic arteries, had aortofemoral arteriography *via* the left axillary artery. His coagulation studies showed prolonged bleeding (26 percent of normal). During the procedure, a small but diffuse hematoma developed and increased in size after catheter removal. A pressure dressing was applied for twelve hours. After its removal, the hematoma suddenly increased in size and the patient developed progressive loss of sensory and motor function of the hand. His radial pulse remained palpable, although slightly decreased. Two hours later, surgical evacuation of the hematoma and suture of a small tear in the punctured artery were performed. Shortly afterwards he regained complete sensory and 85 percent motor function, while three days later, neurological functions were normal.

Case ii. A 61 year old man with advanced atherosclerosis, hypertension (190/110 mm Hg), and occlusive iliofemoral disease had an aortofemoral study *via* the left axillary artery.

Table VI

INCIDENCE OF COMPLICATIONS IN RELATION TO AGE, ARTERIOGRAPHIC RISK FACTORS, AND TYPE OF INFUSION DRUG IN 20 PATIENTS WITH SELECTIVE CHEMOTHERAPY BY THE TRANSAXILLARY ROUTE; STATISTICAL EVALUATION: $P>.5$

	No. of Patients	Complications	
		No.	Percent
Age above 50	9	5	55
Advanced atherosclerosis	8	4	50
Hypertension	6	3	50
Bleeding tendency	6	4	66
5-Fluorouracil Bleomycin	15	4	26
Streptokinase	5	3	60

Diagnostic arteriography was followed by transluminal recanalization of a right superficial femoral artery occlusion (*via* the femoral route). In connection with the angioplasty, the patient received 4,000 units of heparin intraarterially. After the axillary catheter was removed, a local hematoma developed during manual compression. Twelve hours later, this had become quite large and the patient noted weakness and numbness of his left hand in the distribution of the median nerve. Although these symptoms gradually improved over the next two days, a week following the study he developed a pulsatile mass at the axillary puncture site, with a decreased radial pulse and recurrent signs of median nerve dysfunction. At surgery, a 4 cm pseudoaneurysm was removed. The median nerve extended across the pseudoaneurysm and appeared atrophic. Postoperatively, there was only minimal neurological improvement and 18 months later he still had partial motor loss and hyperesthesia.

In correlating the incidence of complications with the type of study done (Table I), the fewest complications were found with aortofemoral arteriography (six percent minor, 1.5 percent major complications), followed by visceral arteriography (13 percent minor complications), coronary arteriography (24 percent minor and four percent major complications), and thoracic aortobrachiocephalic arteriography (24 percent minor and five percent major complications). These differences were statistically significant ($P<.025$). With respect to the possible bearing of catheter size on complication frequency (Table II), the facts were: 7 French, 24 percent minor and four percent major complications; 6.6 French, 8.9 percent minor, 1.8 percent major complications; 5.4 French, 17 percent minor complications. These differences were statistically insignificant. Catheter exchanges correlated to a significant degree ($P<.025$) with complications, particularly minor ones. Procedures requiring but one catheter led to minor complications in 5.7 percent of patients and major complications in 1.4 percent; while 22 percent and 25 percent minor complications rates and 3.7 percent and three percent major complication rates were noted in procedures done using two or three catheters, respectively (Table III). Complication frequency also correlated with arteriographic risk factors (Table IV). Without these, minor complications occurred in only three percent. Hypertension and bleeding tendencies increased the incidence of minor hematomas to 33 percent and 50 percent, respectively. Aortic arch atherosclerosis was associated with minor complications in seven percent and with major complications in 1.4 percent of patients. With multiple risk factors, minor complications occurred in 21 percent and major complications in 5.3 percent. The incidence of complications in patients with multiple risk factors was significantly greater than that in patients with no risk factors ($P<.01$).

In the 20 patients who had selective chemotherapy *via* an axillary catheter, there were three minor complications (15 percent) and four major complications (20 percent). No local infection occurred. One patient who had 5-Fluorouracil therapy lost his radial pulse on the eighth day of infusion, but regained it after catheter removal. Two patients receiving selective streptokinase therapy had local hematomas without consequences. A patient whose transaxillary catheter had been advanced into the external carotid artery had a stroke twelve hours later. In three patients the catheterized axillary artery occluded, one while the patient was receiving selective streptokinase (Fig. 1). Two of the foregoing patients were operated upon with return of function. In the third patient, whose artery occluded after 70 days of 5-Fluorouracil therapy, the thrombus was expressed manually at the time of catheter removal, with complete recovery.

In relating complication frequency and the duration of indwelling catheters, most problems were encountered during the first two weeks of therapy (Table V). Interestingly, there were two patients, women 41 and 38 years of age, who had no complications despite catheters in place for nine and twelve months, respectively. Complications (both minor and major) were significantly more common in patients over

50 years (55 percent as compared to 18 percent in those under 50), and in those on streptokinase therapy (60 percent as compared to 26 percent in those receiving 5-Fluorouracil or bleomycin). Patients with arteriographic risk factors also had more complications: advanced atherosclerosis, 50 percent; hypertension, 50 percent; and bleeding tendencies, 66 percent; as compared without these risk factors: 25 percent, 28 percent and 21 percent of patients, respectively (Table vi). These differences were not statistically significant.

DISCUSSION

The small size of the axillary artery (compared to the femoral) and its close relationship to the brachial plexus make percutaneous axillary catheterization more hazardous than femoral: the axillary artery is more susceptible to spasm and occlusion than the femoral, and its closeness to nerves in a common neurovascular sheath makes the consequence of small hematomas much greater than in the femoral artery. Bleeding within the sheath or a hematoma around it can easily lead to brachial plexus compression and functional impairment, possibly permanent. The incidence of complications of transaxillary diagnostic catheterization requiring surgical countermeasures has been reported as more than ten times higher than with the femoral route.[5] Comparing the complications encountered in this series with those in a series of 445 transfemoral coronary arteriograms also done at this center,[7] the transaxillary route had a five times greater risk of minor complications and about twice the risk of major complications. With respect to selective chemotherapy, we have had twice as many minor complications using the axillary as the femoral route; similarly, the axillary route had a 20 percent incidence of major local complications; the transfemoral route none.[6]

The rate of reported complications in percutaneous axillary catheterization varies greatly. Experience clearly plays an important role. A reported series limited to only 21 studies was associated with minor complications in 24 percent and major complications in 9.5 percent.[16] Larger reported series (*i.e.*, over 100 transaxillary studies), were associated with major complications in 0.6 percent to 3.2 percent.[5,8,10,13,15,18] In the largest reported series with 1,762 procedures, the incidence of minor complications was only 1.6 percent and major 0.5 percent.[12] Our own complication frequency is relatively high; eleven percent minor and two percent major. This, we believe, reflects our strict criteria as to what constitutes a minor complication. We have included minor hematomas and briefly weakened pulses, since, however benign, they are also potential sources of major complications and must be closely followed. We suspect our complication rate also reflects our role as a teaching institution, since of the 220 procedures, 215 were done by a total of 19 different trainees.

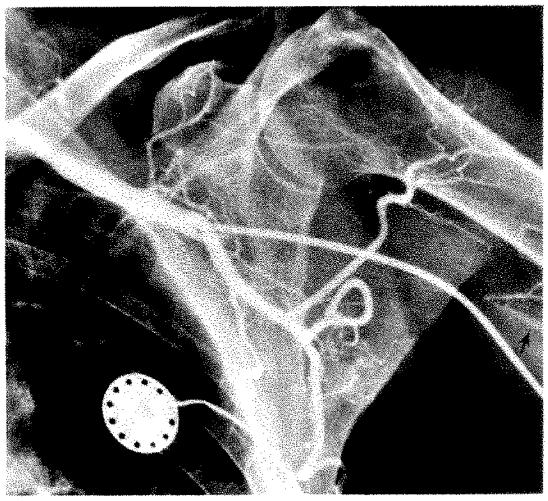

Fig. 1. Occlusion of the axillary artery in a 73 year old man with indwelling catheter for 66 hours for selective streptokinase therapy of the iliac artery thrombosis. The axillary artery is occluded from the site of puncture to the origin of the subscapular artery. There is reconstitution of the brachial artery (arrow) distally to the puncture site *via* collaterals from the subscapular artery branches.

Analysis of the incidence of complications in transaxillary catheterization has shown that risk increases with catheter size.[5] Our series suggests a similar relationship, but the differences lack statistical significance. According to our analysis, risk is significantly related to the number of catheter exchanges and thereby the type of procedure and the presence of arteriographic risk factors such as atherosclerosis, hypertension, bleeding tendencies, particularly in combination. We did not evaluate the role of obesity, but are convinced it adds to the risk of axillary catheterization by increasing the difficulties of arterial puncture and control of postprocedure bleeding.

We strongly endorse the recommendation of others that prompt surgical intervention be done for symptomatic vascular or neural injuries.

In minimizing the risks of transaxillary catheterization, the need for meticulous, careful catheterization technique has been emphasized by all who have studied the matter.[5,8,10,12,15,18] We agree and suggest the following specific measures:

Contraindications: Bleeding tendencies, hypertension, obesity, decreased axillary pulses, particularly in combination, are relative contraindications to axillary catheterization. Should it be required despite their presence, the possible emergency need for postprocedure vascular surgery should be given practical consideration.

Heparin: We do not give intra-arterial heparin for axillary catheterization[17] (unlike femoral catheterization, where it is done routinely). The higher incidence of delayed bleeding with intra-arterial heparinization for the transfemoral route[1] led us to limit the use of heparin to the addition of 1,000 u/100 cc of flushing solution.

Catheters: By virtue of common sense, if not statistical proof, catheters should be no larger than required. Catheter exchanges should be minimized, and the use of a "universal" multi-purpose curve is desirable. In our experience, a slight curve (about 60°) at the catheter tip has been suitable for most selective abdominal studies. For aortofemoral studies, we use a "hooktail" catheter with about a 45° curve 2–3 cm from the tip and multiple side holes.

Side: The left axillary artery is best used for studies distal to the aortic arch, for coronary arteriography,[14] and for indwelling catheter placement. The right axillary approach is advantageous for arch aortography, especially if combined with selective brachiocephalic studies. If possible, the right axillary artery should not be used for indwelling catheters because of a greater risk of cerebral embolization secondary to fibrin deposition.

Puncture Site and Type: Although we speak of an "axillary route," we actually prefer to puncture the brachial artery near its transition into the axillary. The artery here is more superficial, easier to immobilize during puncture and local manual hemostasis is more readily accomplished afterwards. Moreover, should occlusion occur, it will not be so likely to prevent the development of important collaterals from the outer third of the axillary artery. Puncture is usually done 4–5 cm distal to the humeral insertion of the pectoralis major muscle. One-wall puncture, using an open needle, is, we think, preferable to the through-and-through technique since it halves the potential bleeding sites.

Catheter Guidance: J-tipped guidewires are important in enabling smooth, atraumatic passage through tortuous vessels, in avoiding entry into axillary branches, including the vertebral, and in facilitating catheterization of the descending aorta.[11] To this end, with the curved tip of the catheter at the origin of the subclavian artery and oriented posterolaterally, the guidewire's flexible distal segment (20 to 30 cm) is advanced into the descending aorta. As the more rigid portion of the guidewire enters the descending aorta, the catheter is simultaneously advanced with it. This maneuver enables atraumatic catheterization of the abdominal aorta in most cases, even in the presence of a large, tortuous arch. Rarely have we had to use a guidewire deflector* to direct the catheter into the descending aorta. We flush our catheters every 90 seconds with heparinized solution and in between fill them with contrast medium.

Manual Hemostasis: After catheter removal, manual compression of the arterial puncture site, using one or more fingertips, is applied until complete hemostasis is achieved (usually 10–15 minutes). It is important that this be obstructive, not occlusive, as evidenced by a persistent radial pulse. A nonocclusive pressure dressing is then applied and the arm kept in an elevated position for about four hours.

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Postprocedure Observation: A close watch is kept for the appearance of symptoms and signs in the arm, especially for developing evidence of neurological dysfunction. During the procedure and shortly afterwards, patients often have numbness of the forearm and occasionally weakness of fingers, due to the local anesthesia employed for puncture. This should completely and permanently disappear in one to two hours. The subsequent appearance of symptoms such as tingling, pain, decreased sensation, numbness, or weakness in fingers, hand, or arm constitutes early warning of a possible brachial plexus injury. This can show up hours or even days after the procedure, usually reflecting continued or recurrent bleeding within or around the axillary neurovascular sheath. Early surgical axillary sheath decompression must be done, for this can mean the difference between a permanent neural deficit and normal function.

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ANALYSIS OF CECAL VASCULATURE IN THE SEARCH FOR VASCULAR MALFORMATIONS*

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ABSTRACT:

Four patients with gastrointestinal bleeding due to vascular malformations of the cecum are described with emphasis placed on the clinical, angiographic and pathologic features. Barium enema examinations were negative in all four cases and in three of four early venous filling identified the cecal vascular malformation. Postoperative angiographic studies of the cecal specimens using electron emission radiography were helpful in identifying these small lesions.

The pathologic features and possible pathogenesis of this disorder are reviewed. Angiographic and microscopic studies in a control group of 60 post mortem and surgically extirpated cecums defined the normal circulation of the antimesenteric border. In this group, no vascular malformations were present.

VISCERAL angiography in acute and chronic lower gastrointestinal bleeding has changed our concepts of the causes and sites of bleeding. Within the past five years diverticula of the right side of the colon have been implicated as the most common source of massive lower gastrointestinal bleeding.[7] Another unsuspected source of chronic intermittently massive or moderate blood loss has been uncovered. More than 60 cases of vascular malformations of the cecum and ascending colon, unassociated with Rendu-Osler-Weber disease, have been discovered by angiography since 1970 (Table 1).[1,2,4,6,7,8–12,15–17,20,21,23–25,28,30–33] Since none of the lesions was visible on the serosal surface and 90 percent of them were less than 1 cm in size, it is not surprising that in 1949, Gentry *et al.*[17] found no cecal lesions in a review of 106 cases of vascular tumors and malformations of the bowel among 1,400,000 Mayo Clinic case records.

This report describes four cases of vascular malformations of the cecum diagnosed angiographically, and pathologically proved in three, at our institution during the past 18 months. In view of the fact that only 50–60 percent of vascular malformations of the bowel bleed,[17] a postmortem angiographic study of 60 cecums ensued in an effort to establish the normal angioarchitecture of the cecum and to discover early vascular malformations which might give a clue to pathogenesis.

MATERIAL AND METHOD

Autopsy and surgical specimens free of tumor, infection, and infarction, less than 24 hours post mortem were used. They included 5 cm of ileum and 15–20 cm of ascending colon in continuity with intact blood vessels. The ileocolic artery and vein were cannulated and alternately infused at a constant pressure equal to the patient's systolic pressure with 200–300 cc of warm saline. A barium gelatin mixture which allowed filling of capillaries was used to inject the vessels. It was prepared in a blender by slowly adding 100 gm of Knox type 2136 gelatin and 400 gm of Micropaque powder to 600 ml of hot tap water which had been previously mixed with 5 ml liquified phenol/2-octanol in a ratio 60/40. The mixture was allowed to gel overnight, then stored in the refrigerator. The ileocolic artery was infused at the patient's systolic pressure with the warm barium gelatin mixture first. If the ileocolic vein did not fill in this manner, the vein was subsequently infused with the same solution at similar pressures. The specimen was fixed in ten percent formalin for 24 hours. A conventional roentgenogram of the closed specimen inflated with air was then taken. The specimen was opened along the mesenteric border allowing close inspection of the mucosa. A second roentgenogram was taken using industrex M2 film and the Faxitron unit with a focal spot of 0.5 cm. Careful examination of the vasculature of the antimesenteric border was done, aided by photographic enlargement. Microscopic examination of the area opposite the ileocecal valve was done in selected cases. Sectioning was done in a plane perpendicular to the course of the vessels. Sections were stained with Hematoxylin and Eosin as well as Virhoff Van Gieson stain alternately to distinguish more easily arteries from veins.

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Table I

REVIEW OF THE LITERATURE ON VASCULAR MALFORMATIONS OF THE CECUM AND ASCENDING COLON

Author	Description	Age/Sex	Comment
Arvanitakis, C.[1] (1973)	Phlebectasia of cecum	60 F	3 year history of bleeding
Baum, S., *et al.*[2] (1972)	22 cases presented at RSNA meeting in Chicago		
Boijsen, E., *et al.*[4] (1973)	5 cases		
Casarella, W. J., *et al.*[6] (1974)	2 additional cases		
Case Records MGH[8] (1974)	0.5 cm lateral wall cecum	75 M	Hypertension, cholesterol emboli
Clark, R. A., and Rösch, J.[9] (1970)	1 case		
Cooperman, A. M., *et al.*[10] (1972)	Lateral wall ascending colon	69 F	
	Medial wall cecum	52 F	4 mm size
Corry, R. J., *et al.*[11] (1970)	Ileocecal valve	63 M	Mild aortic stenosis, 4×2 mm
	Multiple erosions cecum with dilated veins	62 M	
	Small cecal ulcer	75 M	
	Mucosal erosions cecum	57 F	
	Multiple ulcers	82 F	
Eisenberg, H., *et al.*[12] (1973)	5 mm cecal ulcer	73 M	15 year history of bleeding
Foster, J. H., *et al.*[14] (1973)	1 case	32 F	Appendiceal stump
Galloway, S. J., *et al.*[15] (1974)	5 cases involving right colon		Associated with aortic stenosis
Genant, H. K., and Ranniger, K.[16] (1972)	2 small ulcers posterior wall cecum	65 F	Had systolic murmur
	Lateral wall ascending colon	66 M	
Klein, H. J., *et al.*[20] (1971)	6 cases		
Margulis, A. R., *et al.*[21] (1960)	Cecum	69 F	20 year history of bleeding
Reuter, S. R., and Bookstein, J. J.[23] (1968)	Hepatic flexure	55 F	
Rösch, J., *et al.*[24] (1972)	2 cases		
Rösch, J., *et al.*[25] (1970)	1 case	69 M	
Showalter, B., *et al.*[28] (1970)	Ileocecal	35 F	Present since age 14
	Cecal	65 M	Large
Upson, J. F., *et al.*[30] (1971)	2 small lesions ileocecal area	65 M	3 year history
Van der Ghinst, M., *et al.*[31] (1971)	Two (0.5 and 1 cm) cecal angiomas	61 M	
Whitehouse, G. H.[32] (1973)	Terminal ileum	65 M	Extravasation of contrast medium
	5 mm ascending colon	62 M	
	Blood submucosa antimesenteric border ascending colon	57 F	Extravasation of contrast medium
Wholey, M. H., *et al.*[33] (1965)	1 case		

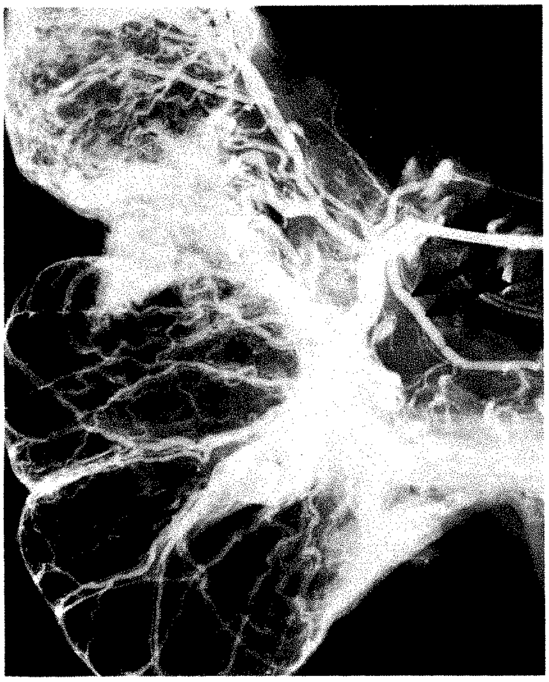

FIG. 1. An injected autopsy specimen demonstrates the 1:1 ratio of artery (arrow) to vein (double arrow), the greater distensibility of the cecum as compared to the ascending colon, and the difference in caliber between arteries and veins.

RESULTS

Of 60 specimens examined, 39 were of good enough quality to permit comment on the mucosal and submucosal vasculature along the antimesenteric border. The remainder of the specimens had poor filling of the peripheral vessels or had extravasation of contrast due to autolysis. Of the 39 specimens, 26 were examined microscopically. The age distribution of the specimens was 41 to 98 years with an average of 66.

The ileocolic artery courses toward the ileocecal valve in the small bowel mesentery. Upon reaching the area of the ileocecal valve the vessel divides, giving off an ascending branch and an ileal branch. The main vessel continues, giving off an appendiceal artery and an artery which forms an arcade by anastomosing with the ascending branch of the ileocolic artery. Distal to this, the vessel divides into four to six anterior and posterior vasa recta which fan out over the cecum (Fig. 1). This vasa recta, as well as those arising from the ascending branch of the ileocolic artery, travel subserosally until at variable distances proximal to the antimesenteric taeniae they obliquely pierce the muscularis in an "S" shaped course to become submucosal vessels (Fig. 2*A*). These are the areas where diverticula form, a process which has been eloquently described by Meyers *et al.*[22] As the vessels taper toward each other along the antimesenteric border where they will anastomose with each other, lateral branches are given off which either become end arteries supplying the muscularis and mucosa or anastomose longitudinally with similar vessels arising from adjacent vasa recta. Three to six such longitudinal anastomoses are seen along the antimesenteric border close to the antimesenteric taeniae in a 10 cm segment of ascending colon. Vasa recta anastomose along the antimesenteric border every 0.5 cm to 2.5 cm depending on the degree of distention of the cecum. The blood supply to the mucosa of the juxtamesenteric borders is derived from vasa brevia which are smaller branches than the vasa recta. They also originate from the ascending branch of the ileocolic artery or from the vasa recta close to their origin. There are between one and four vasa brevia for each vas rectum. These are end arteries which immediately pierce the muscularis as they reach the bowel wall (Fig. 2, *A* and *B*).

The origin of the serosal vasculature is uncertain. However, a fine honeycomb network of vessels can be identified on the serosal surface. Infrequent large serosal veins course across the network in a haphazard manner.

The veins are two to three times larger than the arteries and run parallel to the vasa recta in a 1:1 ratio. Although the veins vary in size from specimen to specimen, they are uniform in size throughout the specimen equidistant from the mesenteric border save for the cecum. Since the cecum is more distensible than the ascending colon, the vessels which supply the

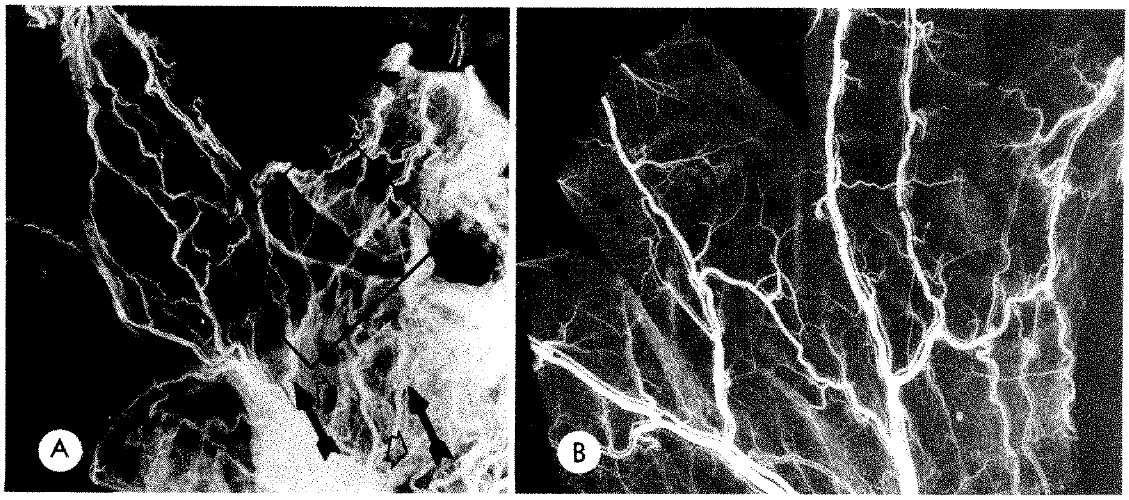

Fig. 2. (*A*) The specimen is opened along the mesenteric border to demonstrate the gradual tapering of the vasa recta such that the vessels along the antimesenteric border of the ascending colon and cecum are of the same caliber. The vasa brevia are indicated by an open arrow and the "S" curve of the vasa recta as they change from subserosa to submucosa by a black arrow. (*B*) Magnification of the antimesenteric border of the cecum shows the longitudinal and transverse anastomose of the vasa recta.

cecum are longer (Fig. 1). They taper more gradually so that the veins which run along the juxtamesenteric borders of the cecum are larger than those of the ascending colon. However, once the vessels reach the antimesenteric border, the arteries and veins of the cecum and ascending colon are of the same caliber (Fig. 2*A*).

The tortuosity of the vessels depends on the state of distention of the bowel and the age of the patient. The more contracted the circular muscles are, the more serpentine the vessels. As the patient ages, the vessels lose their elasticity and become more tortuous as well.

Microscopic examination of 26 normal cecums along the antimesenteric border with sections taken longitudinally, perpendicular to the course of the vessels demonstrates vessels of uniform size in the plane of sectioning. The veins are larger than the accompanying arteries (Fig. 3). As the vessels arborize and become smaller, it becomes difficult to distinguish artery from vein. Distinction cannot be made between pre-capillary arterioles, capillaries, and post-capillary venules. The vessel may reach 30 μ as it pierces the muscularis mucosae. However, in the absence of hyperemia due to prolonged shock, local inflammation, or severe mucosal autolysis, the capillaries remain small.

Two surgical specimens of a bleeding diverticulum were examined in the manner described above. A fresh thrombus was seen in the artery just proximal to the point of rupture in both cases. Local hyperemia manifested by an increase in submucosal vascularity was noted. The submucosal veins were dilated and thin walled,

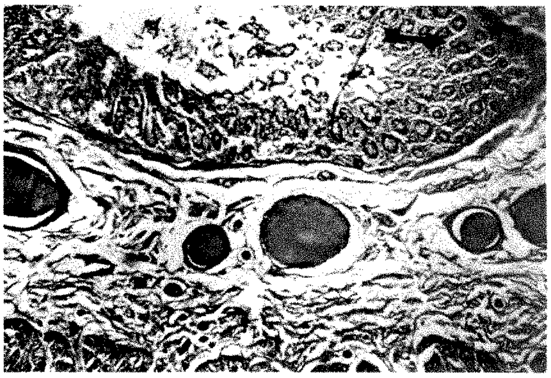

Fig. 3. Microscopic examination of a normal cecum using Virhoff Van Gieson stain (×45) shows vessels of uniform size in the plane of sectioning. The veins are larger than the arteries. The capillaries are filled with contrast material (arrow).

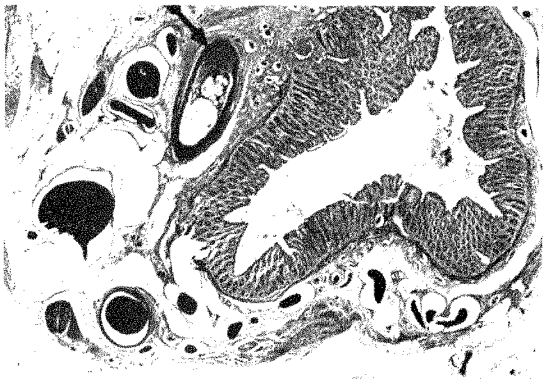

FIG. 4. A bleeding diverticulum (×45) shows a thrombus in the bleeding artery (arrow) at this level of sectioning. The submucosal veins are markedly dilated as are some mucosal capillaries.

but the arteries were the same size as those supplying the adjacent bowel. The mucosal capillaries were engorged (Fig. 4).

Extensive venous ectasia involving the veins of the serosa, muscularis and submucosa, as well as capillary dilatation, was noted throughout the specimens of two cases with a history of prolonged heart failure and one case of portal hypertension secondary to Laennec's cirrhosis (Fig. 5).

A cluster of abnormally dilated but intact veins was seen opposite the ileocecal valve, along the antimesenteric border in one postmortem specimen. An 86 year old woman with a long history of hypertension treated with salutensin and digoxin presented with signs and symptoms of a right-sided stroke, having suffered from several strokes previously. There was a vague history of melena and an appendectomy in the past. Postmortem angiography showed a vein slightly larger than expected along the antimesenteric border opposite the ileocecal valve. Sectioning disclosed a cluster of three abnormally dilated veins which elevated, but did not occupy, the mucosa. Only one normal sized accompanying artery was identified. Small arteries in adjacent submucosal areas were occluded by cholesterol emboli.

REPORT OF CASES

CASE 1. A 44 year old Black woman with a long history of alcohol abuse, biopsy proved nutritional cirrhosis without portal hypertension, had ten admissions to St. Luke's Hospital Center over a five year period for recurrent moderately severe lower gastrointestinal bleeding manifested by maroon colored stools often containing clots. She had mild hypertension in addition to a basilar systolic heart murmur. Repeated endoscopy of the upper gastrointestinal tract to the level of the second portion of the duodenum showed no source of bleeding. The frequency and severity of the bleeding episodes increased requiring multiple transfusions. Conventional roentgenographic examinations of the gastrointestinal tract were repeatedly normal. Exploratory laparotomy was unrevealing. Angiography during a quiescent period showed early venous filling from a slightly enlarged branch of the ileocolic artery supplying a corkscrew collection of vessels in the cecal tip. At surgery no abnormality of the cecum could be seen on the serosal surface. The terminal ileum and ascending colon were removed and handled in a manner similar to the autopsy specimen. On opening the cecum a 2.5 cm area of tortuous submucosal vessels associated with an enlarged draining vein was seen on the antimesenteric border of the cecal tip. Roentgenograms disclosed two slightly enlarged arteries leading to a vascular network composed of a large sinusoidal vein from which many tortuous smaller veins and an enlarged draining vein emanated (Fig. 6; and 7). Multiple sections alternately stained with Hematoxylin and Eosin and with an elastic stain failed to demonstrate an anatomical arteriovenous fistula. The lesion was composed of

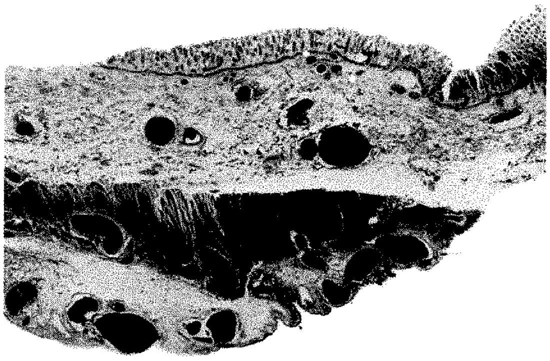

FIG. 5. A section of the antimesenteric border of the cecum in a patient with portal hypertension demonstrates dilated veins throughout the wall of the bowel as well as dilated capillaries (×18).

a large cluster of veins which occupied the submucosa and traversed the muscularis mucosae to invade the mucosa. The remaining mucosa was thinned and atrophied so that only a single layer of columnar epithelium covered the apex of the lesion (Fig. 8). The veins lost their cylindrical shape as a result of eccentric loss of the muscularis and elastic lamellae. In some areas, the elastic lamellae became thickened and lost sharpness at the edges. Some of these veins contained non-occlusive thrombi. However, there was no inflammatory response in or around the lesion. The vasa recta were located at the periphery of the lesion.

Case ii. A 48 year old woman with biopsy proved untreated eosinophilic granuloma of the lungs was admitted with a history of passing bright red blood and clots per rectum on one occasion ten years ago, on a second occasion one year ago and intermittently for six weeks following two weeks of non-specific diarrhea. She required two units of blood and oral ferrous gluconate to maintain a hemoglobin of 10 gm percent. She had a normal prothrombin time, platelet count, bleeding time, and partial thromboplastin generation time on several occasions. Liver function tests as well as conventional roentgenograms of the gastrointestinal tract revealed no abnormality.

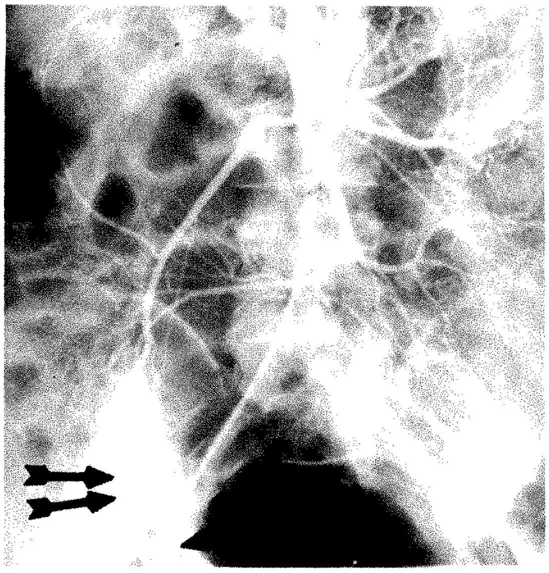

Fig. 6. Case i. The vascular malformation is visualized (single arrow) on the antimesenteric border of the cecum. An early draining vein (double arrow) is seen during the arterial phase of the superior mesenteric arteriogram.

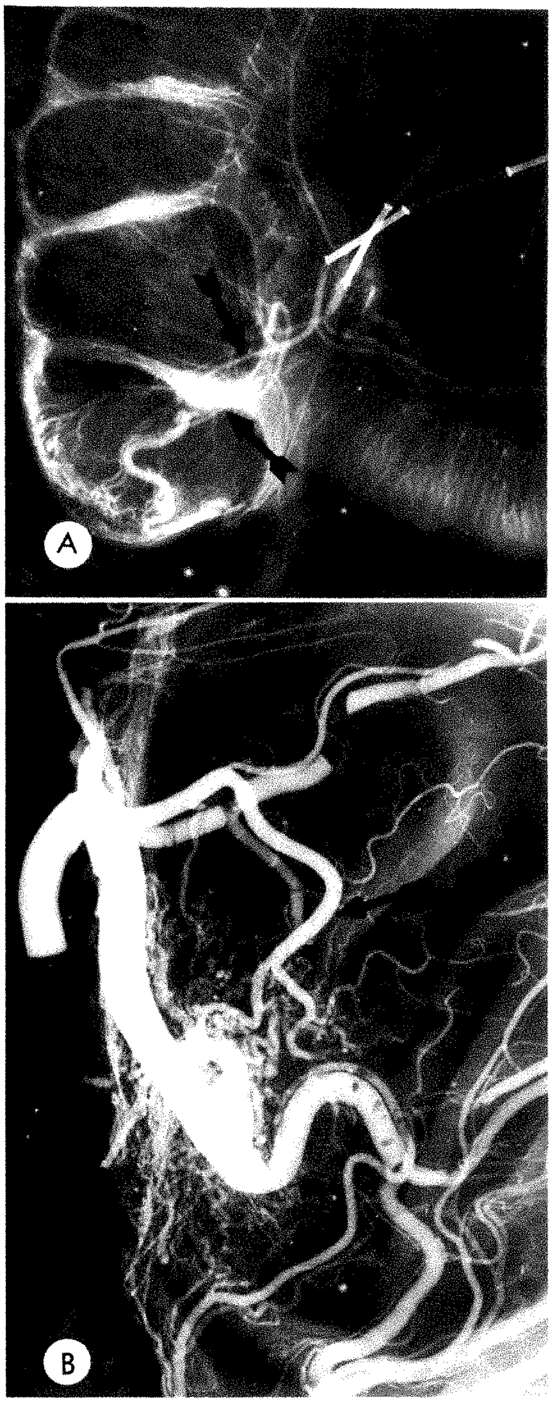

Fig. 7. Case i. (*A*) Angiography of the inflated surgical specimen demonstrates slight enlargement of the feeding vasa recta (arrow) from both juxtamesenteric borders with marked enlargement of the draining vein. (*B*) Magnification (×3.6) shows the extent of dilated tortuous veins which arborize like a medusa's head around a large draining vein. The accompanying vasa recta (arrow) supply the vascular malformation.

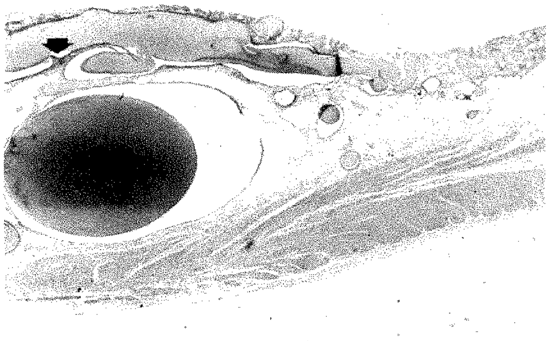

FIG. 8. Case I. Microscopic (×10) examination demonstrates dilated mucosal capillaries. The mucosa is encroached upon by thin walled ectatic veins. Patchy areas of the normal venous wall composed of smooth muscle and an elastic layer remain (arrow).

A superior mesenteric arteriogram, performed during a bleeding episode, demonstrated a prominent artery leading to the lateral wall of the cecum in association with an early draining vein and a suggestion of extravasation of contrast material into the lumen of the bowel (Fig. 9). Resection of the cecum was carried out.

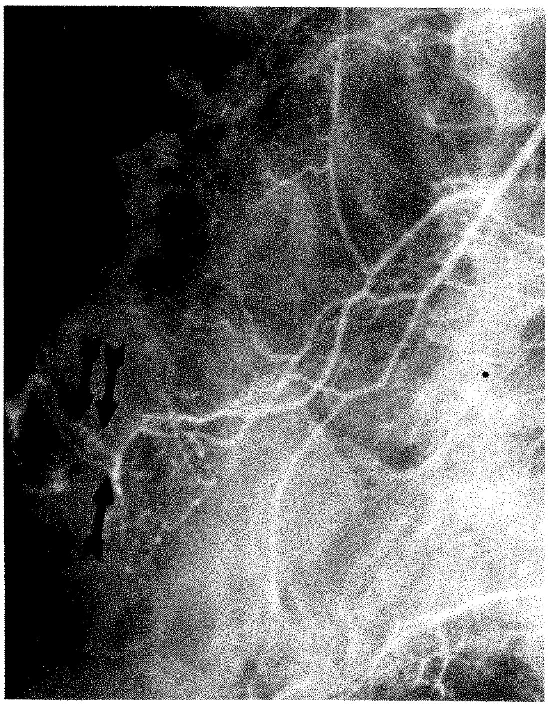

FIG. 9. Case II. The feeding artery (arrow) is enlarged due to increased flow. The contrast along the lateral wall of the cecum is extravasation. An early draining vein is identified (double arrow).

The injected surgical specimen showed only a tortuous, slightly enlarged vein terminating abruptly on the antimesenteric border (Fig. 10). On opening the specimen, a 2 mm ulceration was seen at the point of origin of the dilated vein and a 4 mm cluster of dilated vessels was visible through the mucosa beneath the ulcer. The microscopic findings were the same as those described in Case I save for the extent of the lesion which measured 4 mm.

CASE III. An 84 year old male with a 20 year history of hypertension, aortic stenosis, intermittent atrial fibrillation, and gout, treated with reserpine, digoxin, and allopurinol, was noted to have iron deficiency anemia ten years prior to admission. Guaiac positive stools were first noted eight years prior to admission and frank rectal bleeding requiring four subsequent hospitalizations for transfusions began two years prior to admission. Physical examination was unremarkable except for the previously noted harsh basilar systolic murmur associated with a carotid pulse of slow ascent. Liver function tests and coagulation studies were all within normal limits. Multiple barium examinations of the gastrointestinal tract showed only extrinsic pressure on the greater curvature of the antrum which was felt to be a leiomyoma or lipoma. Repeated endoscopy during bleeding episodes confirmed extrinsic pressure on the antrum and a deformed duodenal bulb, but no bleeding was seen in these areas.

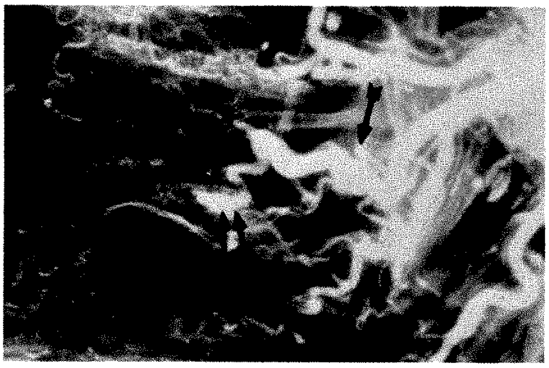

FIG. 10. Case II. Magnification (×2.4) of the opened injected specimen demonstrates only a large tortuous vein (double arrow) with absence of the normal tapering along the antimesenteric border. A normal artery (arrow) accompanies the vein.

A superior mesenteric arteriogram performed during a bleeding episode demonstrated a 4×1 mm amorphous blush along the lateral wall of the cecum which began during the late arterial phase and persisted through the venous phase of the arteriogram (Fig. 11). An early draining vein was not identified. Pitressin infusion was begun as outlined by Baum *et al.*,[3] but the patient pulled out the catheter after four hours of perfusion and re-bled. A right colectomy was performed. The specimen was injected and roentgenographed. However, the vascular malformation was seen only on magnification views (Fig. 12). Localization was aided by the presence of 4×0.5 mm ulceration over the lesion.

Microscopic examination showed the same lesion as previously described. At the periphery of the lesion, the mucosal capillaries were double the size of capillaries in areas away from the vascular malformation. Although serial sectioning through the lesion was performed every 8 μ, an arteriovenous communication was not identified. However, the previously described amorphous blush along the lateral wall of the cecum represented bleeding from a 4×0.5 mm mucosal ulceration at the periphery of the vascular malformation. Immediately beneath the ulcer in the submucosa was a small thrombosed artery with dilated pre- and postcapillary vessels in the vicinity (Fig. 13).

CASE IV. A 68 year old woman had her first episode of rectal bleeding while hospitalized for active pulmonary tuberculosis. She required four units of blood. Evaluation demonstrated a normal colon to the cecum by barium enema examination and colonoscopy. The only abnormality on a superior mesenteric arteriogram was an early draining vein arising from the lateral wall of the cecum (Fig. 14). She stopped bleeding and was transferred to a chronic care hospital for the tuberculosis.

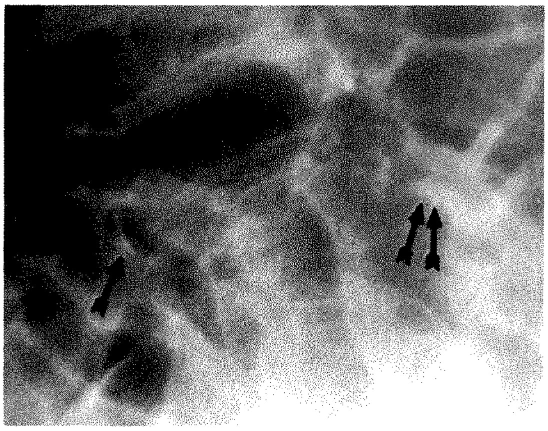

FIG. 11. Case III. Extravasation of contrast material is seen along the lateral wall of the cecum (arrow). The vein (double arrow) did not appear early.

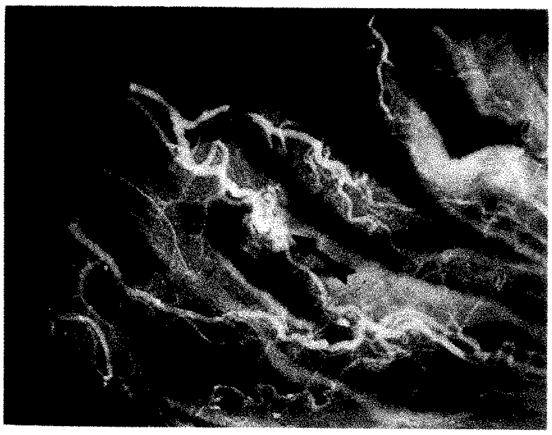

FIG. 12. Case III. The vascular malformation (arrow) was identified only on the angiogram of the specimen (×2.8). Localization was aided by the presence of a 4 mm ulceration over the malformation.

DISCUSSION

The diagnosis of vascular malformations of the cecum and ascending colon should be strongly suspected when a patient between the ages of 40 and 85 presents with chronic intermittent bleeding from the lower gas-

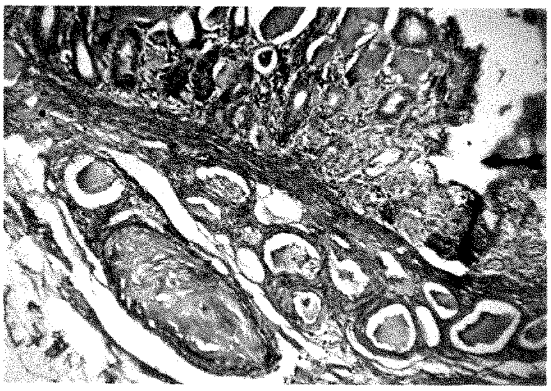

FIG. 13. Case III. Microscopic (×100) examination demonstrates a thrombosed artery in the muscularis mucosae beneath a 4×0.5 mm ulceration of the mucosa (arrow). Markedly ectatic mucosal capillaries filled with contrast material are seen around the ulcer.

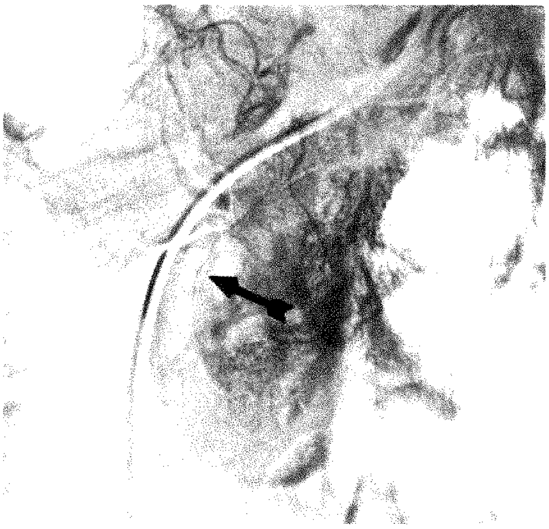

Fig. 14. Case iv. An early draining vein (arrow) is seen parallel to the ileocolic artery during the arterial phase of the superior mesenteric arteriogram.

trointestinal tract together with a negative barium examination. Until recently these patients (Case i) often had a history of a negative exploratory laparotomy prior to angiography because these lesions are not visible on the serosal surface. Selective angiography of the superior mesenteric artery is required to diagnose vascular malformations of the cecum and ascending colon which are invariably located along the antimesenteric border. In order to better visualize individual vessels leading to the antimesenteric border of the bowel, we distend the colon with air prior to performing the examination. Magnification technique is frequently necessary because 90 percent of the lesions are less than 1 cm in size. Identifying an enlarged, early draining vein during the late arterial phase of the angiogram is the most important angiographic finding in making the diagnosis of vascular malformation of the bowel.

Extravasation of contrast material is rarely seen in vascular malformations of the cecum and ascending colon probably because of the slow, intermittent nature of their bleeding.[3] However, two of the four patients (Case ii and Case iii) presented here, were actively bleeding during angiography. This was manifested by staining in a small area along the antimesenteric border opposite the ileocecal valve which lasted through the venous phase of the angiogram. In Case ii a large, early draining vein was identified, but this was not apparent in Case iii. Therefore, the diagnosis could be made only on the angiogram of the opened specimen because the only indication of an abnormality of the mucosal surface was a 0.5×4 mm ulceration over the vascular lesion. In contrast, the vascular malformation of Case i was clearly visible on the angiogram and on the mucosal surface of the injected specimen. It measured 2.5 cm and was supplied by two minimally enlarged arteries at the periphery of the lesion. The draining vein was markedly enlarged. The diagnosis in the fourth case, while presumptive, rests on the finding of an early draining vein on the superior mesenteric arteriogram in the face of normal barium enema examination and a negative colonoscopy to the level of the ileocecal valve.

The pathogenesis of vascular malformations of the cecum is unknown. However, several hypotheses may be explored by examining the microscopic sections of the vascular malformations in our three cases. Baum and associates[2,3] have proposed that the initial stimulus for the development of vascular malformations is increased intraluminal pressure within the bowel leading to submucosal shunting from artery to vein. This process, if sustained, leads to ectasia and venous proliferation, and in turn, produces local ischemia of the mucosa. Accordingly, submucosal shunting should render the mucosa less vascular. However, this thesis is not supported by our findings. In Case iii a wide network of dilated mucosal capillaries is overlying the vascular malformation. Increased, rather than decreased, vascularity is thus present in this case. Moreover, careful sectioning of all three cases failed to reveal anatomic arteriovenous communications in the submucosa. This raises the possibility that the vascular malformation represents a local area of increased blood flow which results in dilatation of capillaries and veins.[5] The potential for increase in splanchnic blood flow is large. Experimentally induced hyperemia in animals increases the blood flow by 40 percent. Obliteration of the precapillary sphincter tone can increase intestinal blood flow by 400 percent.[13]

The histologic similarities between the vascular malformations of the cecum, bleeding diverticula, and venous engorgement as seen in portal hypertension and congestive failure are striking. Capillary and venous engorgement are seen in all three conditions. In bleeding diverticula and vascular malformations of the cecum, the venous engorgement is limited to the submucosa of the lesional area which is felt to be related to increased blood flow. Venous engorgement in portal hypertension and congestive failure is seen throughout the colon and involves all the layers of the bowel.

Ischemia of the mucosa could result from a pressure phenomenon created by the encroachment of the large submucosal veins on the mucosa (Case I), or, as in Case III, by thrombosis of submucosal arteries. Another mechanism to be considered is rapid flow through the mucosal capillaries which creates a functional shunt. This prevents normal exchange of metabolites and thereby causes mucosal ischemia.[13]

Analogies have been made between isolated vascular malformations of the cecum and ascending colon and the vascular lesions of the bowel seen in Rendu-Osler-Weber disease. The angiographic appearance and the age at which these lesions are manifest are very similar.[19,29] Two types of vascular lesions of the bowel have been described in Rendu-Osler-Weber disease: an angioma which is nodular, and one which resembles spider angiomas of the skin seen in cirrhosis.[27] It is the latter lesion visible on the mucosal surface which has been compared to vascular malformations of the cecum.[8,32] There are few detailed descriptions available of the relationship between arteries and veins in the vascular malformations of the cecum. A spider angioma has a central artery which anastomoses with multiple veins to form a medusa's head pattern.[27] The vascular malformations of the bowel we have observed have one or two feeding arteries at the periphery of the malformation which send branches centrally. The central vessel is a large draining vein as in Case I. Despite similar microscopic findings of ectatic thin walled veins in the submucosa of both lesions, the lack of other similarities suggests that isolated vascular malformations of the cecum and the lesions of Rendu-Osler-Weber disease have no pathogenetic mechanism in common.

It has been difficult to correlate the development of these vascular malformations with other disease states. The cases described in this communication had totally different intercurrent diseases. Two of our patients had murmurs of aortic stenosis. Case I had a nonsignificant basilar murmur. Case III died of postoperative complications which permitted close inspection of the aortic valve. The valve was tricuspid and mildly calcified. The valve area was 1 cm^2 which was probably not hemodynamically significant. The left ventricular hypertrophy was thought to be secondary to prolonged hypertension. Seven additional cases of aortic stenosis and cecal vascular malformations have been reported.[11,15,16] It has been suggested that bleeding vascular malformations are responsible for the increased incidence of occult gastrointestinal bleeding seen in aortic stenosis.[15]

The study of autopsy and surgical cecal specimens has allowed us to describe the angioarchitecture of the antimesenteric border in detail. There is a 1:1 ratio of artery to vein. There are many anastomoses along the mesenteric border between the vasa recta of opposite walls of the colon. In addition, longitudinal anastomoses between parallel vasa recta distal to the antimesenteric taeniae ensure continued perfusion of the bowel during peristalsis.[26] As a result, in order to produce ischemia of the bowel the vascular occlusion must occur in small arteries in the submucosa or within the mesentery.

The angiographic and histologic study of the cecums obtained at autopsy is fraught with several problems. Autolysis of the mucosa occurs at a variable rate post mortem. This results in extravasation of contrast material and obliteration of the normal architecture. Moreover, postmortem spasm prevents proper filling of the vessels. Finally, the functional state of the patient's cardiovascular system at the time of death may influence the degree of vascularity of the bowel wall.

In this study no vascular malformations of the cecum were found in 39 autopsy and surgical specimens representing a control group of patients without a history of gastrointestinal bleeding of unknown cause. One case demonstrated a local increase in the number of dilated veins surrounding a single submucosal artery. This was associated with cholesterol emboli to adjacent arteries. Increased flow due to shunting away from the embolized areas is postulated.[5] This has been suggested as the mechanism responsible for the development of vascular malformation of the cecum in a patient with extensive cholesterol emboli to the vasa recta of the cecum.[8]

SUMMARY

An angiographic study of 39 cecums and a microscopic study of 26 postmortem cecums were undertaken to define the anatomy of the antimesenteric border where the majority of vascular malformations occur. Our findings are in agreement with the detailed descriptions of the vascular supply to the jejunum and distal colon published by Griffiths[18] and Ross.[26]

Four patients with vascular malformations of the cecum are presented in detail to emphasize the diversity of the angiographic and pathologic findings. The histologic appearance of these lesions is similar to the venous ectasia seen in acute localized hyperemia of bleeding diverticula and generalized venous engorgement associated with increased venous pressure. Therefore, the anatomical venous changes observed in vascular malformations of the cecum can be acquired. We postulate that vascular malformations are a result of functional shunting.

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COMPUTERIZED RECONSTRUCTIVE TOMOGRAPHY APPLIED TO BREAST PATHOLOGY*

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ABSTRACT:

Breast tumors can be clearly defined from the surrounding breast parenchyma by the use of computerized reconstructive tomography. Certain types of fibrocystic mastitis also can be distinguished from tumors, but other types of fibrous mastitis and probably fibroadenomas may not be distinguishable from tumors unless contrast material is used.

THE EMI brain scanner was developed and tested clinically in England from 1967 to 1972. Because of its ability to distinguish very small gradations of density, the machine is revolutionizing neuroradiology.[1,4] The same principles of image reconstruction are now being applied to machines that examine the whole body.

In an effort to evaluate the role of computerized tomography in the diagnosis of breast lesions, we examined entire specimens (removed because of carcinoma) immediately after modified radical mastectomy. Other excised specimens of benign tissue were also examined.

MATERIAL AND METHOD

Seven carcinomatous specimens were scanned (Table I). In addition, six specimens of fibrocystic mastitis were examined (Table II). One of the latter was a total mastectomy specimen, and five were excisional biopsy specimens. A box designed especially to hold tissue specimens in the EMI scanner was used and has been previously described.[5]

RESULTS

These examinations revealed that the postmenopausal breast consists almost entirely of fat. The attenuation coefficient of fat is in the −50 to −60 range (on the EMI scale). Premenopausal breast parenchyma contains more prominent glandular and ductal elements interspersed with fat. This results in attenuation coefficients that fluctuate between −50 and 0. The pattern is nonuniform, as contrasted to the relatively uniform coefficients of from −50 to −60 associated with the postmenopausal

TABLE I

ATTENUATION COEFFICIENTS OF EMI SCANNING IN SEVEN CASES OF BREAST CANCER

Case	Mean	Highest	Lowest
1	21.9	26	16
2	26.6	34	21
3	23.5	26	19
4	21.0	28	17
5	20.7	25	18
6	17.0	29	2
7	19.4	27	15

TABLE II

ATTENUATION COEFFICIENTS OF EMI SCANNING IN SIX CASES OF FIBROCYSTIC BREAST DISEASE

Case	Mean	Highest	Lowest
1	15.3	22	10
2	47.2	101	−5
3	22.2	26	17
4	15.6	26	7
5	15.2	20	9
6	21.4	34	11

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* Presented at the Seventy-sixth Annual Meeting of the American Roentgen Ray Society, Atlanta, Georgia, September 30–October 3, 1975.

From the Mayo Clinic and Mayo Foundation, Rochester, Minnesota.

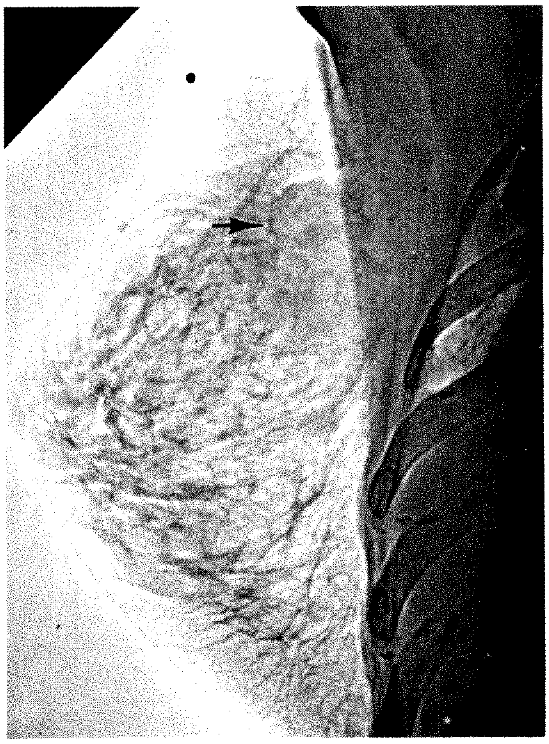

Fig. 1. Xeromammogram demonstrating 3 cm cancer (arrow) in tail of right breast. Remaining breast parenchyma is of dense premenopausal type.

fatty breast and with the subcutaneous layer of fat in the premenopausal breast.

Carcinoma. The seven carcinomas, being composed of nonfatty tissue, had average attenuation coefficients that ranged from +17.0 to +26.6, and were in sharp contrast to the surrounding fatty tissue (Fig. 1–7).

Fibrocystic Disease. The simple mastectomy specimen removed for fibrocystic disease showed, at pathologic examination, diffuse cystic changes with average attenuation coefficient of +15.3 (Fig. 8; and 9). The remaining examples of fibrocystic mastitis were excisional biopsy specimens, and their average attenuation coefficients ranged from +15.2 to +47.2 (Table II).

DISCUSSION

The conventional roentgenogram uses a field of roentgen rays which ranges from 10×10 cm to 30×50 cm. Radiation passes through the patient or the part to be imaged and strikes an intensifying screen of calcium tungstate, which directly exposes a film of silver halide. Essentially, this combination of film and screen has not changed significantly since the discoveries by Roentgen in 1895 and by Edison in 1896. Most of the information transmitted in the roentgen-ray beam is lost by the film-screen combination because of two problems:

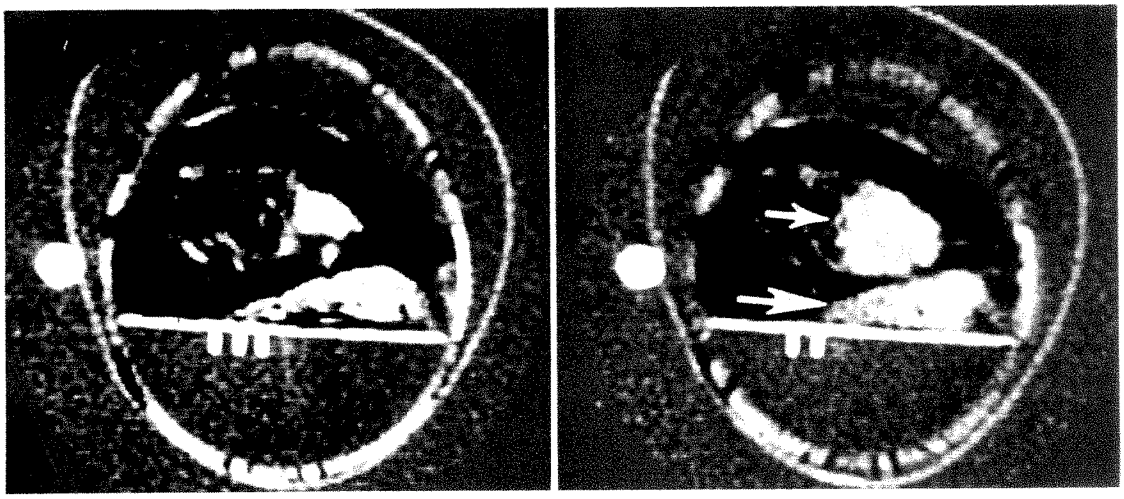

Fig. 2. Computerized scan of specimen shows round tumor whose absorption coefficient averaged +21 EMI units. Tumor (small arrow) lies directly above pectoral muscle (large arrow) and is separated from it by a layer of fat and fascia. Absorption coefficient of muscle averaged +25.7. Dense normal glandular parenchyma has been almost filtered out by setting the level at +20 with a window width of +20.

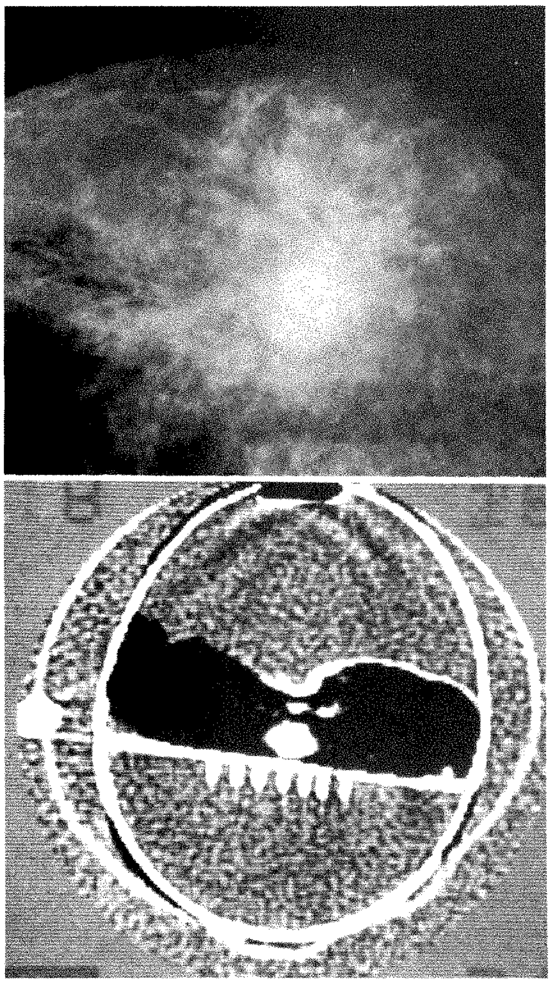

FIG. 3. Specimen roentgenogram is shown above the reconstruction made with Faxitron specimen x-ray machine, which uses a low kV roentgen-ray beam for maximal contrast. Absorption coefficient for tumor averaged +21.3 units. Fat is −50 and is presented as a black background. Note thickened retracted skin above tumor.

1. A large percentage of the photons that emerge from the patient are not captured by the film-screen combination. For this system, further improvement in statistically limited contrast resolution can be accomplished only by increasing patient dosage.

2. Scattered radiation has a significant detrimental effect on the quality of a roentgenogram, as pointed out recently by Ter-Pogossian and associates.[7] Reducing the size of the beam (to as low as 4×4 mm) makes detectable soft-tissue density differentials as low as two percent. However, a field size of 4×4 mm is too small to be of clinical use.

The EMI scanner overcomes both of these problems and can resolve density differences that approach 0.5 percent.[2,3] Rather than using the film-screen combination, this scanning device uses a sodium iodide crystal that has an efficiency of 90 percent in photon capture. The diameter of the collimator leading to this sodium iodide crystal is approximately 3×13 mm. This has enabled attenuation coefficient differences in brain tissue of less than two percent to be easily distinguished, thus making brain tumors, hematomas, infarctions, and other intracranial diseases primarily visible for the first time.

In EMI head scans, we can distinguish

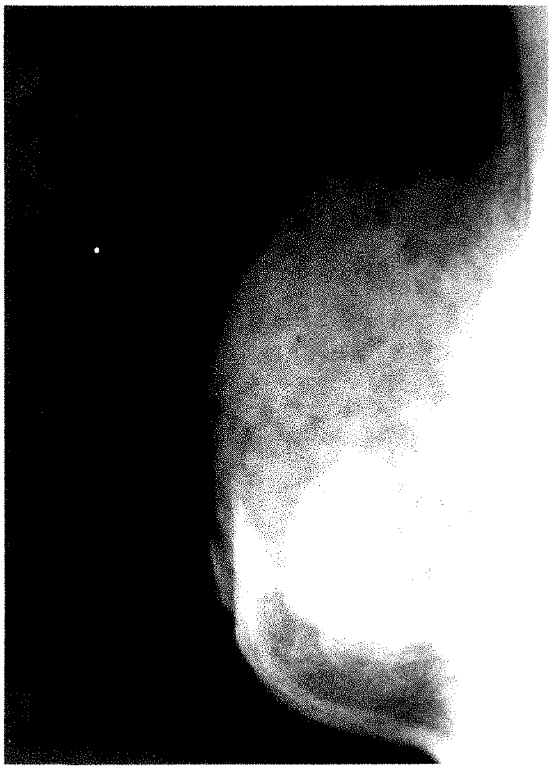

FIG. 4. Mammogram, lateral view, right breast, of 75 year old woman with dense fibrous mastitis. Ill-defined tumor involves lower half of breast and is somewhat obscured by surrounding fibrous mastitis.

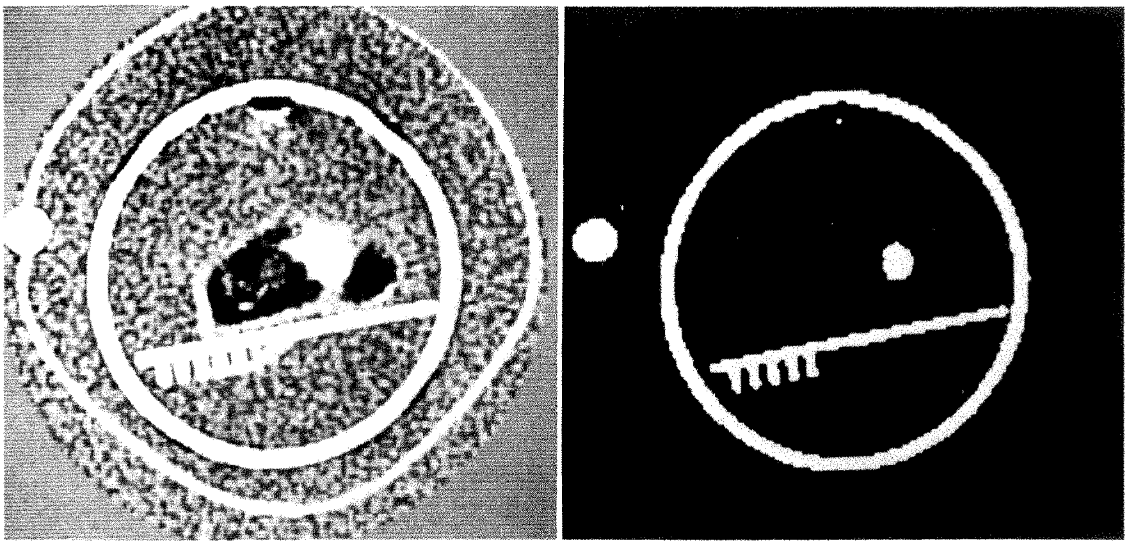

FIG. 5. EMI scan of whole breast specimen (needle biopsy of Grade III adenocarcinoma). By various degrees of filtering, tumor can be brought out from background and dense fibrous mastitis can be completely suppressed. In most tumors studied, absorption coefficients averaged approximately +22 units. This was the densest tumor in this group, averaging +28 units.

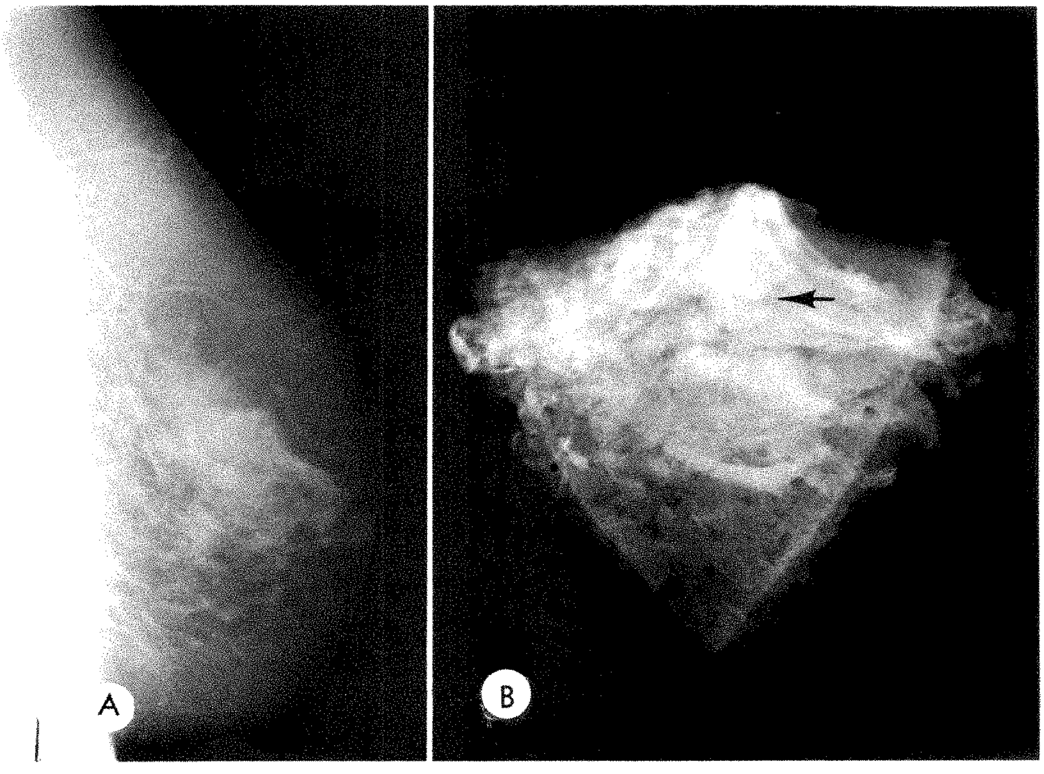

FIG. 6. Mammogram of left breast. (*A*) Lateral view and (*B*) specimen roentgenogram. Left breast removed because of dense fibrous mastitis. The surgical pathologist unexpectedly found a 1 cm cancer (arrow) under the nipple. One-half of the lesion was removed for microscopic examination. Specimen roentgenogram does not definitely display the remainder of the tumor.

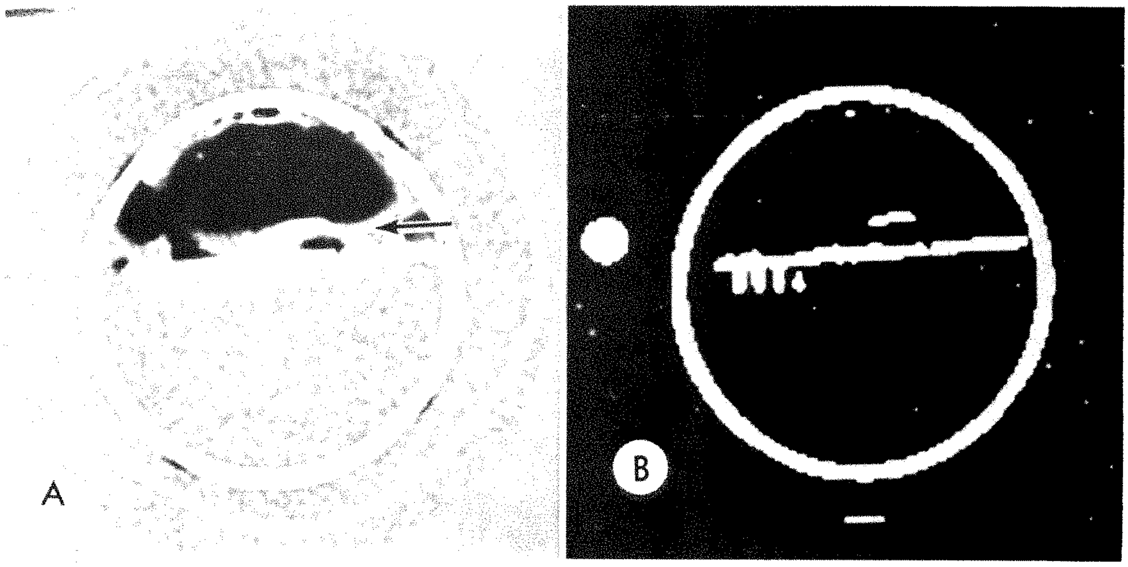

FIG. 7. EMI scan of specimen. (*A*) Unfiltered picture shows flat strip of tissue (arrow). (*B*) Filtered picture (window width on measure, level at +20). Solid rectangle represents remainder of tumor in whole mastectomy specimen.

abnormal brain density from normal brain density if there is a difference of 3 or 4 EMI units (0.5 percent). In the breast, however, the average density of the tumors is about +22 units of attenuation coefficient, whereas the surrounding fat has an average of −50 or −60, making a total difference of approximately 80 units. This is an enormous difference and literally makes the breast tumor stand out as stark white on a black background.

The results indicate that certain cases of fibrocystic mastitis can be differentiated from malignant tumors. However, in one

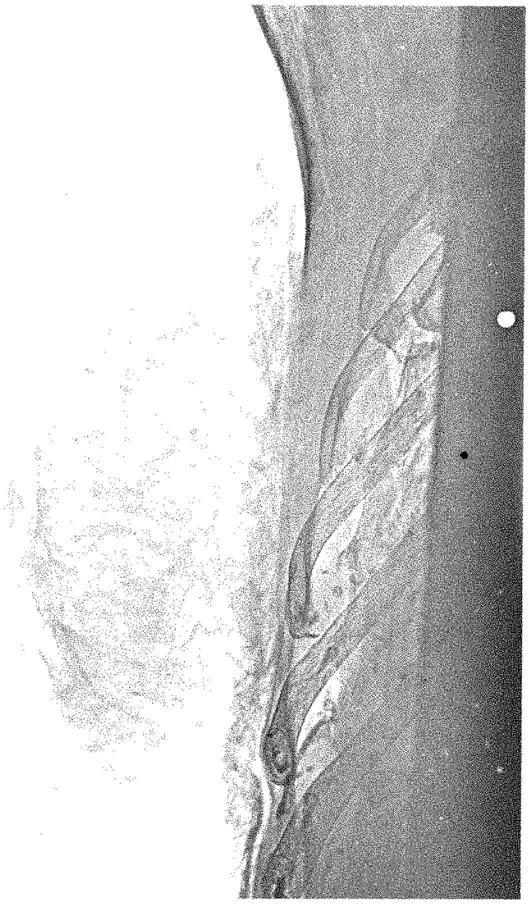

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FIG. 8. As postulated from EMI experience with brain disorders, cysts in breasts should be distinguishable from solid tumors by simple filtering. This patient had her right breast removed six months previously because of carcinoma. Remaining left breast is diffusely involved with fibrocystic mastitis, as seen on xeromammogram. No tumor is visible, but small malignant lesions are easily obscured in such breasts. Clinically, the breast was hard and lumpy, and cancer could not be excluded. Therefore, a left simple mastectomy was performed.

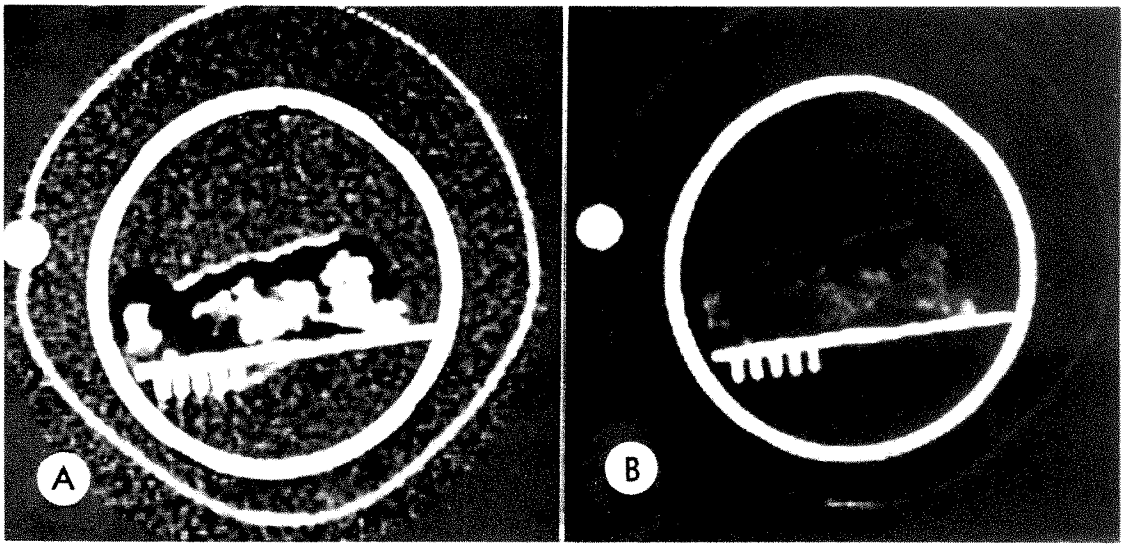

FIG. 9. (*A*) EMI scan shows diffuse cystic disease, window level set at 0. (*B*) Window level was set at +20, and cysts, having attenuation coefficients of approximately +15, have been filtered out.

case in which mammography showed an isolated dominant 3 cm mass and EMI scanning showed an attenuation coefficient that averaged +21.4 (similar to that of a malignant tumor), pathologic examination revealed a dense area of fibrous mastitis (Fig. 10; and 11).

Although it would seem that we could not differentiate among a breast tumor with attenuation coefficient of +20 or +30, fibrous mastitis, and a fibroadenoma, all of which may have similar densities, our experience with scanning the brain reveals that certain tumors, especially vascular ones such as metastatic lesions and meningiomas, become considerably more dense if they are scanned after the injection of one of the conventional diatrizoate compounds such as Renografin. The vascularity of these tumors seems to make them more dense in the EMI scanner after injection. We postulate, therefore, that breast carcinoma, which generally is a vascular lesion, should respond similarly to the injection of contrast material, whereas fibrous mastitis, which is an inactive dense fibrous formation and is relatively avascular microscopically, should change very little after the injection of contrast medium.

Whether fibroadenomas can be dis-

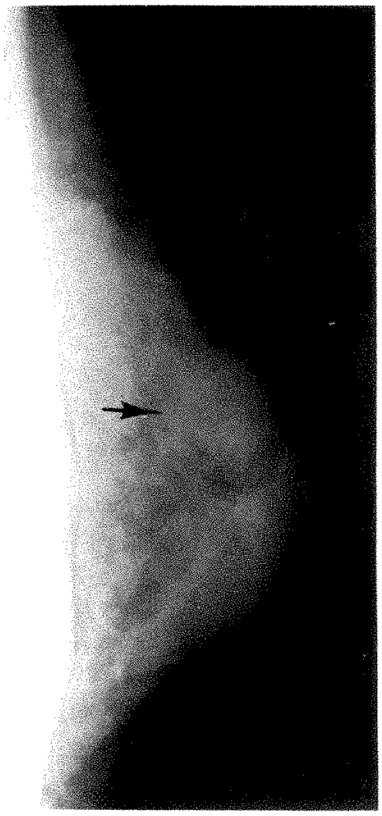

FIG. 10. Smooth, 3 cm, isolated, dominant mass (arrow) in upper half of left breast in 47 year old woman with diffuse fibrous mastitis. Thermogram was positive in upper outer quadrant of left breast. Fibrous mastitis was confirmed by excisional biopsy.

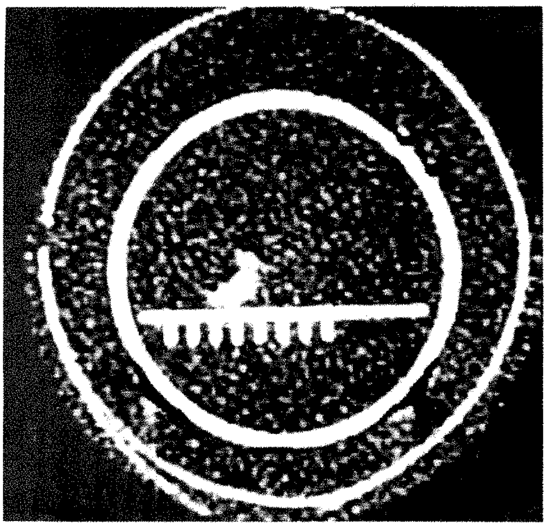

Fig. 11. Computerized reconstruction of the excised specimen shows an average attenuation coefficient of +21.4 units, which would make it impossible to distinguish this lesion from cancer by simple filtering. It is postulated, however, that this mass would change very little after injection of contrast material but that a malignant tumor of similar size would increase its attenuation coefficient because of its higher vascularity and metabolic activity.

tinguished from malignant tumors is not certain as yet because the response of the fibroadenoma to contrast agents is unknown at this time. We have distinguished cysts from malignant lesions without using contrast material because the absorption coefficient of cysts is approximately +15. Although we have not scanned examples of fat necrosis, which can mimic a malignant tumor on a mammogram, we believe that since the necrotic areas do contain fat, albeit altered, the density should be low and they should be distinguishable without the use of contrast medium.

The tumors examined in this study ranged between 1 and 5 cm in diameter. We believe that tumors between 0.6 and 1 cm in diameter should be visible by this method even though they may be buried in dense premenopausal breast tissue or in areas of fibrous mastitis (Fig. 6; and 7). Ultimately, even smaller tumors or diffuse infiltrative tumors of the breast, even though they may have no mass effect, may be detectable by the aid of computer comparison analysis.[6] Our data from breast studies have motivated the General Electric Company to embark on the development of a prototype computerized tomographic system specifically designed to examine the breast.

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EFFICACY OF PNEUMOGYNECOGRAPHY IN THE DIAGNOSIS OF MEYER-ROKITANSKY-KÜSTER-HAUSER SYNDROME*

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ABSTRACT:

Twelve patients with Meyer-Rokitansky-Küster-Hauser syndrome were examined by means of pneumogynecography. The results obtained disclose the great diagnostic value of the method in this disorder.

CONGENITAL absence of the vagina associated with rudimentary double uterus was known to Avicenne and Albucasis. However, Meyer was the first modern author to describe the anomaly, while Küster, Rokitansky and Hauser reported their own clinical observations as well as previously published data. The syndrome is associated with numerous abnormalities. There are a variety of malformations of the female genital tract, a normal development of female secondary sex characteristics, normal ovarian function, anomalies in the development of the kidneys, ureter and skeleton,[3,6] chromosomal abnormalities,[2,4,5] and dermatoglyphic phenomena.[7] The basis for the development of this syndrome is obscure and its diagnosis is associated with considerable difficulty, principally because of difficulty in determining the precise state of the internal genital organs.

We have examined patients with the Meyer-Rokitansky-Küster-Hauser syndrome by means of pneumogynecography and present this information in an attempt to simplify the diagnosis.

MATERIAL AND METHOD

Twelve patients with the syndrome were investigated by pneumogynecography. Other examinations included investigation of the circulating hormones, chromosomal studies, and the dermatoglyphic status, as well as conventional examinations of the chest, pelvis, skeleton, and urinary tract by intravenous urography. The air studies of the pelvis were carried out under fluoroscopic control with amplification and television monitoring. Records were made on a 70 mm camera.

After insufflation of gas, the patients assume the knee-chest position on the table, with the knees separated about 35 cm and with exaggeration of the lordosis. This results in axial projection of the pelvic organs. In addition, oblique views as well as tomograms were made in some of the patients.

RESULTS

In eleven of the twelve patients, the uterus was not demonstrable. In these,

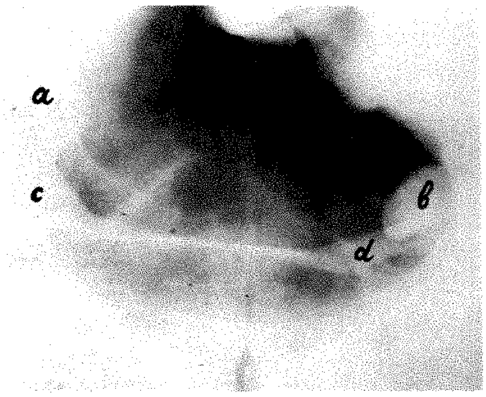

Fig. 1. Duplicated rudimentary uterus. a = Right ovary; b = left ovary; c = right uterus; d = left uterus.

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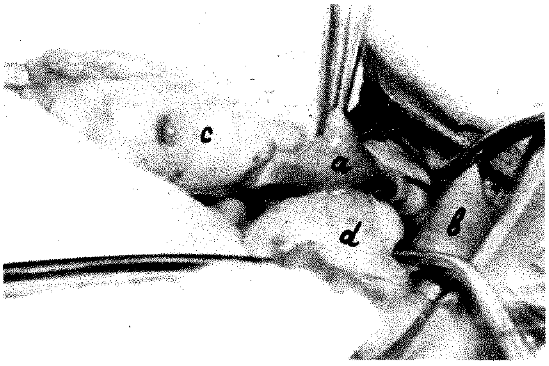

FIG. 2. Surgical specimen. a = right uterus; b = left uterus; c = right ovary; d = left ovary.

careful observation disclosed two small tissue masses, one on each side below the ovary and close to the bony pelvis. These were of homogeneous density, round, fixed in position, and each measured about 1.5 by 1.5 cm (Fig. 1). In three of these patients the masses were confirmed surgically to be a rudimentary double uterus (Fig. 2). Absence of the suspensory uterine ligament led to an empty appearance of the pelvis. In the twelfth patient the uterus was visualized as a thickened band of homogeneous density 1.5 by 3 cm situated in the middle of the pelvis (Fig. 3). In none of the women was there complete absence of the uterus.

DISCUSSION

This malformation is considered to be a defect in the development of the Muellerian tubes at various periods of development and to a variable extent. When the development of the uterus ceases early in development of the embryo, the uterus appears as a double rudimentary structure: when the Muellerian tubes have fused and development stops, the uterus develops as a small mass in the middle of the pelvis.

In eleven patients the ovaries appeared normal roentgenographically with localization in the lateral part of each side of the pelvis. This position made oblique studies indispensable. In one of the patients under examination, an orange size mass arose from the right ovary, and at laparotomy this was shown to be a dermoid cyst, as had been suggested by the roentgen examination (Fig. 4). The normal appearance and function of the ovaries explained the normal puberty, secondary sex development, and normal hormonal findings in these patients.

The use of television control and the 70 mm camera proved to be particularly suitable for this type of study in which small structures were being visualized, as this permitted ready selection of the most suitable position.

Dosimetric studies showed that these patients received about one-tenth the radiation with a 70 mm camera that they would have received by conventional roentgenography.

Since the determination of the state of the internal genital organs is of vital im-

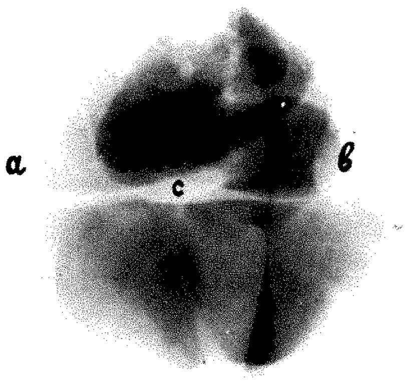

FIG. 3. Single rudimentary uterus. a and b = ovaries; c = uterus.

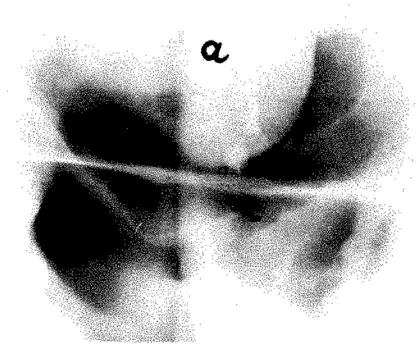

FIG. 4. Dermoid cyst of ovary. a = ovarian dermoid cyst; b and c = uterus.

portance in the precise diagnosis of this syndrome, this method of examination is valuable. There were practically no complications and the study was well tolerated by the patients. Use of this method will probably make unnecessary many surgical studies such as exploratory laparotomy or laparoscopy.

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RETROCECAL APPENDICITIS PRESENTING WITH AIR IN THE SUBHEPATIC SPACE*

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ABSTRACT:

Two cases of perforated retrocecal appendicitis presenting with the roentgen finding of an air containing subhepatic abscess are discussed. Although it is an unusual cause for air in the right subhepatic space, retrocecal appendicitis should be considered in the radiologist's differential diagnosis.

CASES of perforative retrocecal appendicitis presenting with the roentgen finding of air in the right subhepatic space are uncommon. We have recently encountered two cases in which the presence of subhepatic air played a decisive role in the diagnosis of clinically unsuspected appendicitis.

REPORT OF CASES

CASE I. (F.R.) A 13 year old white male developed nausea, vomiting, and mid-abdominal pain seven days before hospital admission. Tenderness in the right flank and epigastrium was present on physical examination at the time of admission. His temperature and white blood cell count were elevated. Urinalysis was normal. A supine view of the abdomen showed an extraluminal, oval collection of air overlying the upper pole of the right kidney (Fig. 1*A*). During barium enema examination irritability of the right colon was encountered and an ascending, retrocecal appendix with a distorted tip was opacified. The appendiceal tip was immediately inferior to an abscess in the subhepatic space (Fig. 1*B*). At operation, the diagnosis of perforated retrocecal appendix with a subhepatic abscess was confirmed. The perforated appendiceal tip was within the abscess cavity and the appendiceal base was intact. In addition, multiple, small abscesses were present in the right paracolic gutter. An appendectomy and drainage of the subhepatic and right paracolic abscesses were performed.

CASE II. (W.D.) A 66 year old white male was admitted to the hospital because of right upper abdominal pain of four days' duration. Tenderness to palpation in the right upper abdominal quadrant and right flank was found on physical examination. Rectal examination was normal There was no elevation of temperature or white blood cell count. Plain roentgen studies of the abdomen showed an oval collection of air in the subhepatic space with displacement of the ascending colon medially secondary to exudate in the right paracolic gutter (Fig. 2). A barium meal examination showed deformity of the duodenal bulb without an active ulcer crater. Marked irritability of the right colon during barium examination necessitated the use of intramuscular glucagon. The spasm, however, was unaltered and the cecum consequently was incompletely distended. There was no opacification of the appendix. The roentgen and clinical findings indicated a perforated retrocecal appendix with abscesses in the right paracolic gutter and subhepatic space. At operation, the perforated tip of the retrocecal appendix was lying within the subhepatic abscess cavity. The base of the appendix was intact. An appendectomy was performed with drainage of the subhepatic and paracolic abscesses.

DISCUSSION

The anatomic dimensions of the right subhepatic space and its posterior extension, Morison's pouch, have been previously described.[1,4,6] Briefly, the subhepatic space is located above the upper pole of the right kidney with the inferior surface of the liver forming the anterior boundary and the peritoneal covering of the diaphragm and upper pole of the right kidney making up the posterior border. Inferiorly the space

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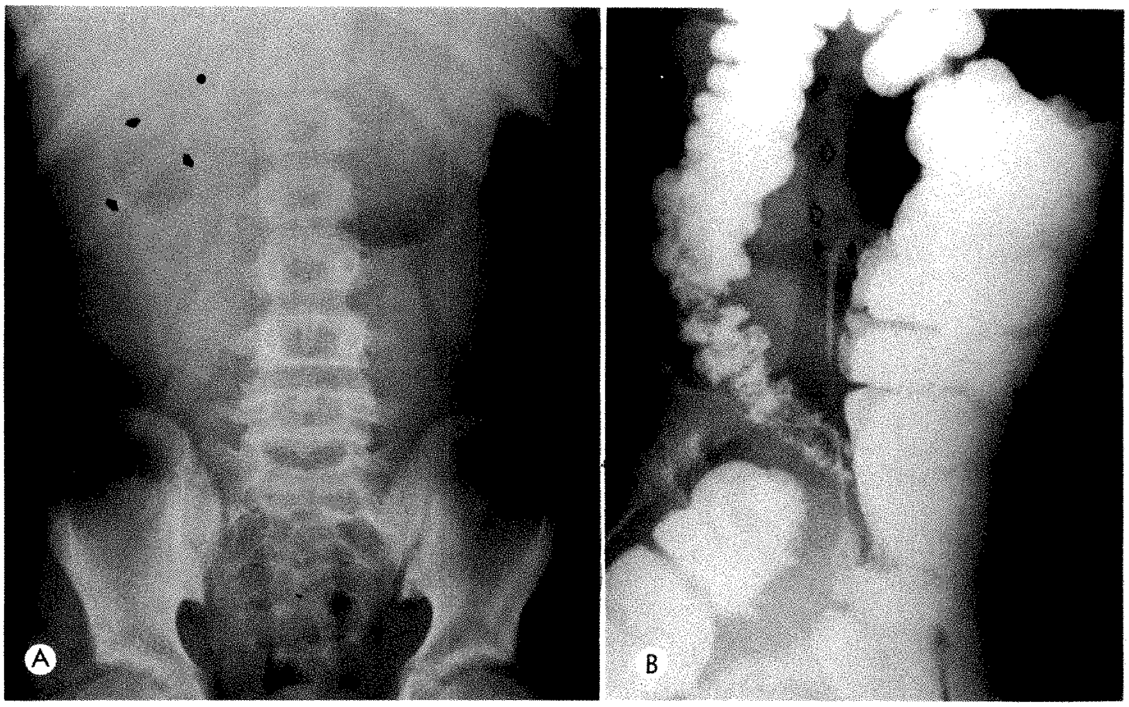

Fig. 1. Case 1. (*A*) Supine abdomen. Air-containing abscess in the subhepatic space (arrows) from a perforated retrocecal appendix. (*B*) Barium enema examination, lateral view. Distorted, perforated tip of the retrocecal appendix (black arrows). Air-containing abscess within the subhepatic space (clear arrows). Note that the base of the appendix is intact.

opens into the peritoneal cavity and is bounded superiorly by the coronary ligament.[6]

One of the most common sources of free air in the right subhepatic space is a perforated duodenal ulcer.[1,6,7] Less commonly, subhepatic air has been reported to originate from a perforated appendix, a perforated sigmoid diverticulum, and from leakage of gastroenteric or ileotransverse colon anastomoses.[1,2,6] An air-containing abscess is another source of subhepatic air and may originate as a complication of enteric perforation or from pathology in the pelvis. Meyers[4] has shown that the preferential flow of inflammatory exudate from the pelvis is up the right gutter into the subhepatic space.

On a supine abdominal roentgenogram, free air in the subhepatic space usually assumes a triangular or crescent shape and overlies the right kidney inferior to the liver edge.[1,3,6,7] Air in a subhepatic abscess will be in the same location but may have a round or oval configuration as in our two cases (Fig. 1*A*; and 2). An air fluid level within the abscess may be demonstrated on upright or lateral decubitus views. Upright, lateral studies of the abdomen will localize subhepatic air posteriorly just in front of the lumbar vertebral bodies (Fig. 1*B*).

The oval configuration of air within a subhepatic abscess may be confused with air in a large duodenal bulb, in a duodenal diverticulum, or within the bowel adjacent to the liver edge. Serial abdominal films, decubitus views, or a small amount of contrast material within the stomach and duodenum should help in the differentiation. Air within the gallbladder, as in emphysematous cholecystitis, may have a similar appearance to a subhepatic abscess. An upright, lateral abdominal view, however, should localize the gallbladder anteriorly as opposed to the posterior position of a subhepatic abscess.

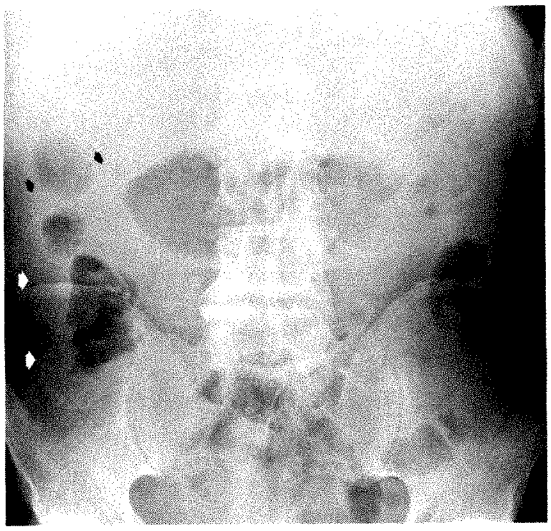

FIG. 2. Case II. Supine abdomen. Abscess in the subhepatic space from a perforated retrocecal appendix (black arrows). Inflammatory exudate in the right paracolic gutter (white arrows) with medial displacement of the ascending colon.

If the radiologist, when confronted with air in the right subhepatic space, at least considers appendiceal disease, the patient may be spared unnecessary diagnostic procedures. In both of our cases, the patient's clinical presentations were not typical for appendicitis and indeed this diagnosis was not considered by their physicians.

In Case I, air in a subhepatic abscess was the only abnormal plain roentgen finding (Fig. 1*A*) and a barium enema was the initial contrast examination because of the patient's negative history for duodenal ulcer. The older patient in Case II, had a past history of perforated duodenal ulcer and a barium meal examination was performed to exclude recurrent perforation. The abdominal roentgenogram on this patient showed air in a subhepatic abscess as well as evidence of abscess formation in the right paracolic gutter (Fig. 2). In both cases, only the tip of the retrocecal appendix perforated distally into the subhepatic space with resulting abscess formation and subsequent retrograde involvement of the right paracolic gutter by inflammatory exudate. Irritability of the right colon present in both patients was most likely secondary to this exudate.[5]

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PULMONARY METASTASES FROM INTRACEREBRAL MENINGIOMA*

DIAGNOSIS BY PERCUTANEOUS NEEDLE ASPIRATION BIOPSY

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ABSTRACT:

A case of metastatic meningioma to the lung is reported and the recent literature reviewed. This case was diagnosed solely by cytologic examination of fine needle aspiration biopsy. Pulmonary metastases are relatively rare and the diagnosis by this method has not previously been reported.

METASTATIC meningioma to the lung is rare, and its diagnosis by any but the usual methods has not yet been reported. This is a report in which such a diagnosis was made by fine needle aspiration biopsy in a patient who in the past had had intracerebral meningioma, and its recurrence following surgery.

REPORT OF A CASE

At the age of 36, eight and one-half years prior to the present admission, the patient was admitted with a chief complaint of right-sided headaches. Physical examination revealed bilateral papilledema, right greater than left, slight right facial weakness, and a decreased right-sided smell sense. An electroencephalogram revealed right frontotemporal slowing, and a brain scan revealed increased activity over the right fronto-parasagittal area. A right carotid arteriogram demonstrated a large mass involving the right frontal lobe in the parasagittal region. A right frontal craniotomy was performed and a right frontal parasagittal tumor was partially removed. The pathologic diagnosis was "meningioma with many mitoses suggesting malignancy." A second stage total excision of the mass and removal of the involved falx was performed one month later with an uneventful postoperative course. Tissue from that procedure revealed "no evidence of tumor, only scarring in the falx." The patient was discharged without medication and did well with only a mildly abnormal electroencephalogram which appeared to be improving. His chest roentgenogram at the time of that admission was negative.

One year postoperatively he experienced his first seizure, grand mal in nature, complicated by a fracture of the left scapula. He was treated with Mysoline which was discontinued after he was without further seizures for two years. His electroencephalograms continued to improve and his brain scan was reported as negative.

Three years later, (four and one-half years prior to the present admission) he began to experience increasingly severe left occipital headaches relieved by aspirin. One year later, he was admitted for his third hospitalization with a one day history of a slight fever and a generalized seizure without localizing signs. Physical examination was within normal limits. An electroencephalogram at that time revealed seizure activity in the right frontotemporal area. On the basis of a strongly positive Arsenic 74 brain scan demonstrating increased activity over the right frontal area, he underwent his third frontal craniotomy. His chest roentgenogram was still normal. At surgery, there was a recurrence of meningioma with dural involvement extending to the sagittal sinus and without evidence of cerebral involvement. Pathologic diagnosis was syncytial meningioma. Postoperatively, he did well except for brief periods of hyperthermia that cleared without specific therapy. He was maintained on antiseizure medication and followed by technetium 99m brain scans (which were reported as nega-

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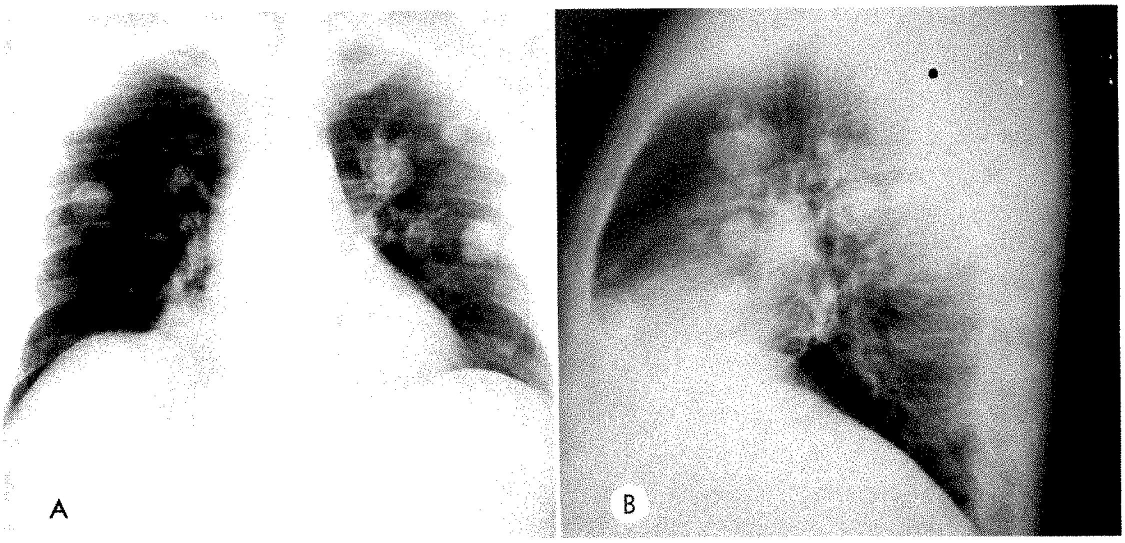

FIG. 1. (*A* and *B*) Posteroanterior and lateral chest roentgenograms showing multiple non-calcified nodules of varying sizes throughout both lungs.

tive) and by electroencephalograms (reported as unchanged). In the three and one-half year interval until his present admission, he was seen twice with seizures, presumed secondary to inadequate medication.

One day prior to admission, he was seen in the clinic complaining of right-sided pleuritic chest pain. A chest roentgenogram revealed multiple pulmonary nodules without calcification, a small right pleural effusion, and no mediastinal lymphadenopathy (Fig. 1, *A* and *B*). Since this was thought most consistent with metastatic disease, he was admitted to the hospital for the work-up of an unknown primary malignancy. His review of systems was negative except for a moderate smoking history. Physical examination revealed a low-grade temperature, dullness with decreased breath sounds at the right base, a pigmented lesion of his right iris, and a small, firm, non-tender left epididymal mass. The only significant laboratory finding was an elevated alkaline phosphatase. His work-up included the following: negative pleural fluid, pleural biopsy and urine cytologies; negative intravenous pyelogram, nephrotomograms, upper gastrointestinal and small bowel follow-through studies, barium enema examination, sigmoidoscopy, iodine-131 thyroid scan, technetium 99m diphosphonate lung scan; negative PPD with positive mumps skin test; a urologic consultant considered the left epididymal mass within normal limits; an ophthalmologic consultant felt that the pigmented lesion of the right iris did not represent melanoma. Because of the abnormalities on the chest roentgenogram, percutaneous fine needle aspiration biopsy was performed on the eighth hospital day and the material was sent for cytologic examination.

DESCRIPTION OF PATHOLOGY

The tumor in the meninges was fibrous in some areas but predominantly highly cellular, lobulated with some whorls, a few psammoma bodies and large areas of necrosis (Fig. 2*A*). Nuclei were vesicular, varied in size and shape, and had large nucleoli. No mitoses and no intranuclear vacuoles were seen.

The cytologic specimens from the aspiration biopsies contained single and grouped cells with variable amounts of cytoplasm, often elongated. Some groups showed whorl formation. Nuclei were large, vesicular, moderately pleomorphic with large nucleoli. Nuclear vacuolation was rare. No psammoma bodies or mitoses were present. Cytologic features resembled those in the brain tissue specimen (Fig. 2*B*).

DISCUSSION

Pulmonary metastasis from meningioma

has been recently reviewed along with all metastatic meningiomas by Karasick and Mullan.[2] They list the first reported case in 1880 by Power and Sweet, and since then 34 cases of metastases to lung have been noted. In a review of Shuangshoti and associates,[4] 25 percent of 31 cases had previous craniotomy, often repeated. Rubenstein[3] states that while any histologic type may metastasize, "three examples submitted in the past five years were all recurrent metastasizing angioblastic meningiomas with cytologic features suggestive of rapid growth."

Meningioma can spread by direct extension into local areas and metastasize in the central nervous system by cerebrospinal fluid pathways. Its trail into the pulmonary bed has not been documented, but one might suspect that it is blood-borne through venous channels. It is noted that in patients with distant metastases where there had been no surgery, some had invasion of the superior sagittal sinus.[1] The finding of such permeation into venous channels is so relatively common at surgery,[3] that its importance must be tempered with the fact that distant metastases are so rare, or at least sub-clinical and undiagnosed. Lymphatic spread has not been shown to be a proved route of spread.

The cytologic characteristics of the cells, chiefly nuclear and cytoplasmic pleomorphism, indicate malignancy, but without the history of meningioma, it may be difficult to establish the type of tumor. The cells resemble those of sarcoma rather than carcinoma. Comparison with the patient's previous surgical specimens reveals striking cytologic similarity and confirms the diagnosis of metastatic meningioma.

Patients with roentgenologic findings suggesting neoplastic lung metastases are now often evaluated by cytologic examination of material obtained by needle aspiration. Although meningioma metastasizes rarely, this diagnosis should be considered both by the radiologist and the pathologist

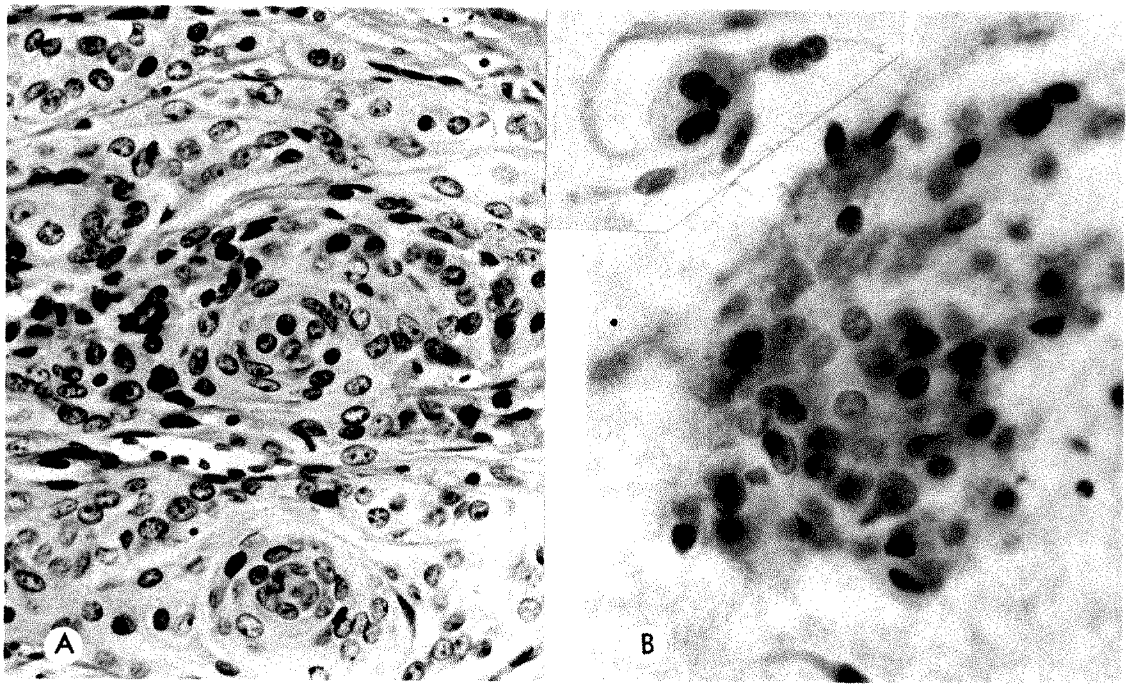

FIG. 2. (*A*) Histologic specimen from previously resected intracranial meningioma showing marked cellularity and pleomorphism. (*B*) Cytologic specimen from fine needle biopsy showing striking similarity to histologic specimen. (Inset shows whorl formation.)

in the presence of a history of intracranial symptoms or previous craniotomy.

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HAZARDS OF THE INTENSIVE CARE UNIT*

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ABSTRACT:

Complications arise in the introduction, maintenance, and use of devices for life support and monitoring in an intensive care unit. Since recognition of such complications is frequently difficult in this clinical setting, the radiologist is often in a position to be the first to detect complications associated with the use of endotracheal and tracheostomy tubes, Swan-Ganz catheters, subclavian catheters, central venous pressure catheters, and intra-aortic balloons.

DURING the past decade many new devices have been introduced to aid in the management of the seriously ill patient. Unfortunately, these life support and monitoring devices are not without hazards of their own. Recognition of the problems resulting from use of these devices is of critical importance in patient management. The clinical examination is frequently difficult and unrewarding, and because of this the radiologist often plays a key role in diagnosis. In order to be of help, however, he must be aware of the potential complications of the devices being used. It is not possible to review every potential complication, but some of the more common ones will be presented, thus indicating the types of problems which must be considered when examining the roentgenograms of these critically ill patients.

VENTILATORY SUPPORT TUBES

The most commonly used life support tubes in the critically ill patient are the ventilatory support tubes—*i.e.*, the endotracheal tube and the tracheostomy tube. The complications encountered with the use of these devices primarily concern poor positioning, and the degree of distention of the balloon cuff.

Incorrect placement is more commonly encountered roentgenographically with the endotracheal tube. Most often the tube is found inadvertently positioned in the right main bronchus.[19] Preference for the right side is attributable to the narrower angle of origin of this bronchus as well as its larger size as compared to the left. Incorrect placement results in varying degrees of obstruction of the left main bronchus by either the tube or its balloon cuff and, consequently, decreased or absent ventilation of the left lung. This in turn can result in rapid and complete atelectasis (Fig. 1).

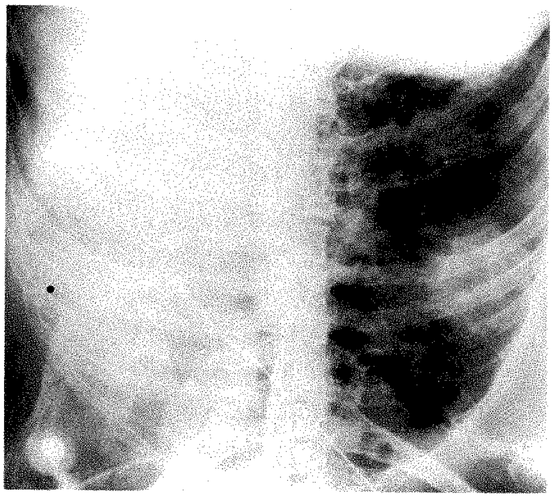

Fig. 1. The endotracheal tube has been inadvertently positioned in the right main stem bronchus with resultant total atelectasis of the left lung. (The bone lesions are secondary to multiple myeloma.)

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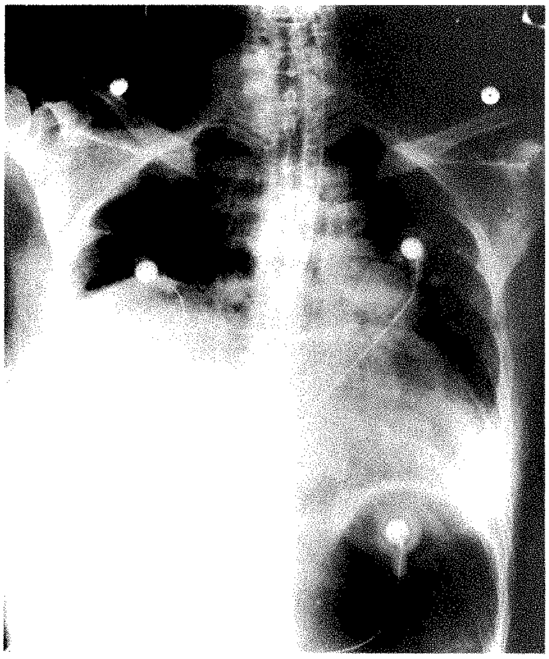

FIG. 2. The endotracheal tube has been inadvertently positioned in the esophagus. Note that it projects to the left of the trachea and that the tip extends beyond the carina. In addition, note the marked gastric distention associated with this malposition.

The rate of collapse is enhanced by the use of increased amounts of oxygen in the inspired gas.[19]

Incorrect placement of the endotracheal tube can occur either at the time of initial insertion, or subsequently, secondary to patient motion and resultant displacement of the tube. Thus, it is important to obtain a post-intubation roentgenogram to ensure that the tube is in a satisfactory position, and to evaluate carefully all subsequent roentgenograms to ensure there has been no displacement of the tube. Satisfactory positioning is generally accepted as having the tip of the tube lying between 3 cm distal to the vocal cords and 2.5 cm proximal to the carina in an adult.

Although inadvertent placement of the endotracheal tube in a bronchus is the most common malposition observed roentgenographically, occasional instances of a tube placed in the esophagus have also been noted. Such placement is usually detected clinically and corrected, but should be considered whenever significant gastric distention is observed (Fig. 2).

Use of positive pressure respirators required a closed ventilatory system and resulted in development of cuffed ventilatory support tubes. The wide-spread use of such tubes led to increased recognition of tracheal injuries related to the cuff itself. Considerable attention has been devoted to this problem in both the surgical and radiologic literature.[3–5,7,12,13,16] Investigation demonstrated that tracheal damage resulted from the high pressure exerted by the balloon cuff on the tracheal mucosa and subsequent pressure necrosis at this site. Clinical studies indicated, however, that if the intracuff pressure could be maintained at 25 mm of Hg or less, significant tracheal damage could be avoided.[4] This realization in turn led to a change from low volume-high pressure cuffs which appear circular on roentgenograms, to the use of high volume-low pressure cuffs which appear rectangular. It is important for the radiologist to be aware of the danger of over-inflation of the balloon cuff, for while it can be easily recognized on the roentgenogram (Fig. 3), it is extremely difficult, if not impossible, to detect clinically prior to the development of tracheal stenosis or severe tracheomalacia.

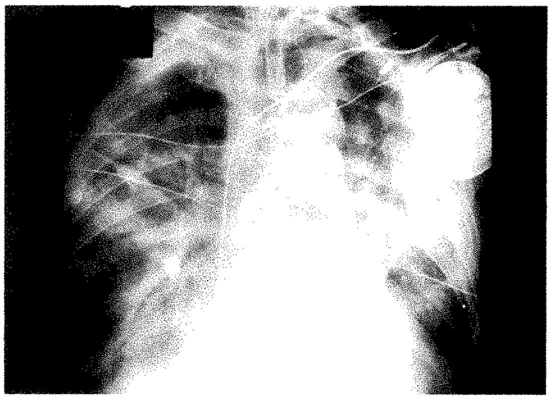

FIG. 3. The tracheostomy balloon cuff is over-distended. Note the circular radiolucency representing the balloon cuff which clearly extends beyond the normal confines of the trachea. This reflects distortion of the trachea by the overinflated balloon cuff.

Recently, several tubes have been introduced which attempt to maintain intracuff pressures below the critical level of 25 mm of mercury.[16] We have encountered, however, several examples of over distention of these balloon cuffs as well (Fig. 4).

FLOW DIRECTED BALLOON TIPPED CATHETER (SWAN-GANZ CATHETER)

In 1970 Swan and co-workers[18] reported a flow directed balloon tip catheter which could be inserted at the bedside and from which pulmonary capillary wedge pressures could be recorded. Use of this catheter and its subsequent modification, which allows measurement of cardiac output as well,[11] greatly facilitated hemodynamic management of critically ill patients. The major roentgenographically detectable complica-

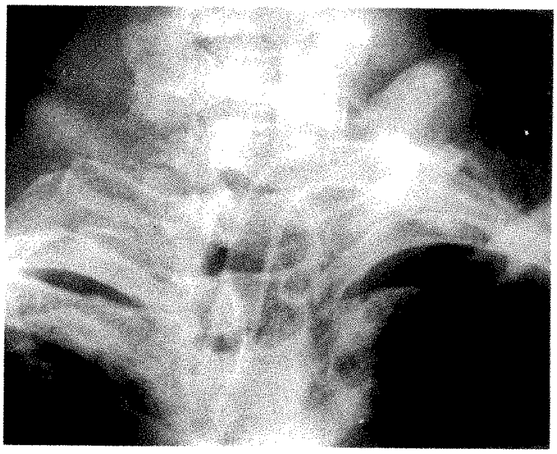

Fig. 4. Over-distention of a controlled pressure cuff which was secondary to inadvertent compression of the external balloon. The lateral margins of the cuff extend beyond the normal lateral confines of the trachea reflecting distortion and distention of the trachea by the cuff.

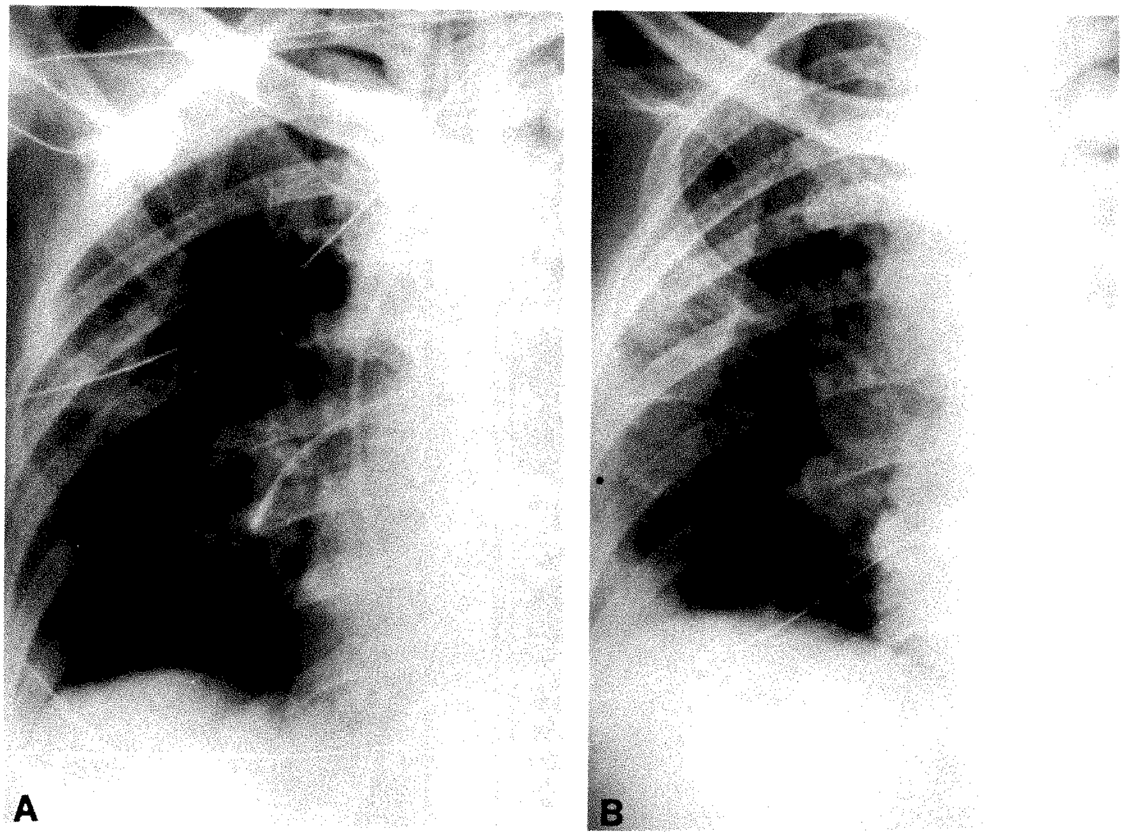

Fig. 5. (*A*) Swan-Ganz catheter positioned in a right basilar segmental artery. (*B*) Follow-up examination two days later demonstrating a pleural based density in the right costophrenic angle with a convex upper border consistent with pulmonary infarction.

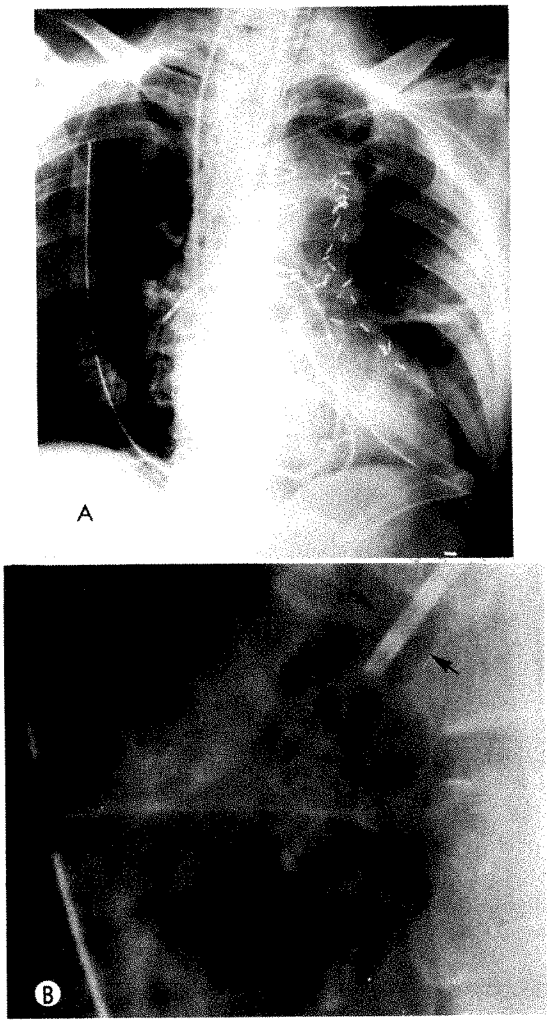

FIG. 6. The roentgenogram (*A*) was obtained because the patient began having multiple premature ventricular contractions (PVC's) following placement of a Swan-Ganz catheter. The catheter is coiled in the right ventricle and the PVC's stopped when the catheter was straightened. Also noted, however, is the fact that the balloon tip (arrows) has inadvertently remained inflated as illustrated on the close-up (*B*).

tion resulting from use of these catheters is pulmonary infarction[10,17] (Fig. 5).

Pulmonary infarction results from either persistent wedging of the catheter tip in a peripheral pulmonary artery or failure to deflate the balloon. Clinical experience suggests that multiple small thrombi develop around the tip of the catheter, as evidenced by damping of the pressure tracing. Flushing the catheter to ensure adequate pressure measurements results in the release of multiple small emboli into the pulmonary arterial circulation. The more peripherally positioned the catheter, the smaller the area of lung subtended by it, and thus the increased chance of infarction resulting from decreased flow through the artery due to obstruction of its lumen by the catheter itself or by the numerous small clots formed at its tip. We have not encountered any incidents of pulmonary infarction in cases in which the catheter has been maintained in a more central pulmonary artery during the times at which pressures were not being obtained. It is presumed that this is because the catheter is not large enough to significantly obstruct the lumen of a larger pulmonary artery, nor is the number of clots sufficient to cause infarction when dispersed throughout the larger pulmonary vascular bed subtended by the central arteries.

It is of particular importance to evaluate the tip of the catheter to ensure that the balloon has been deflated (Fig. 6). Although persistent inflation of the balloon occurs infrequently, it can result in total occlusion of the large pulmonary artery, and consequently, in a significant pulmonary infarction.

SUBCLAVIAN CATHETERS

The subclavian vein, because it is a large vessel and lies in a consistent anatomic location, provides rapid access to the central venous pool in the critically ill patient. Because of the anatomic features of the region, however, percutaneous venepuncture of the subclavian vein entails the risk of many potential complications.[8,9] The vein arches over the medial portion of the first rib to join the internal jugular vein behind the sternoclavicular joint, forming the innominate vein. The subclavian vein is separated from its companion artery as it crosses the first rib by the anterior scalenus muscle. The pleura overlying the apex of the lung is only 5 mm deep to the vein. The technique of catheter placement involves directing a needle backwards, inwards and slightly upwards from the midpoint of the clavicle, aiming toward the sternoclavicular joint.[16] The potential complications are readily apparent and include pneumothorax, entrance into the mediastinal or pleural spaces, and arterial puncture. Prospective studies[1] have confirmed that, as expected, complications are more common in patients whom the procedure is performed "on an emergency basis." Statistically, the most common complication is that of inadvertent arterial puncture which can result in hemothorax and which, on occasion, can require surgical intervention.[15] The next most common complication, and probably the one most frequently noted by the radiologist, is pneumothorax (Fig. 7). Interestingly, because of the complex clinical problems of the patient, this complication may not be recognized on physical examination. An attempt may then be made to place the subclavian catheter on the opposite side and this, too, can result in a pneumothorax. The physician suddenly finds himself dealing with a patient with a bilateral pneumothorax in whom respiration is severely compromised. As a result, it is strongly recommended that a chest roentgenogram be obtained

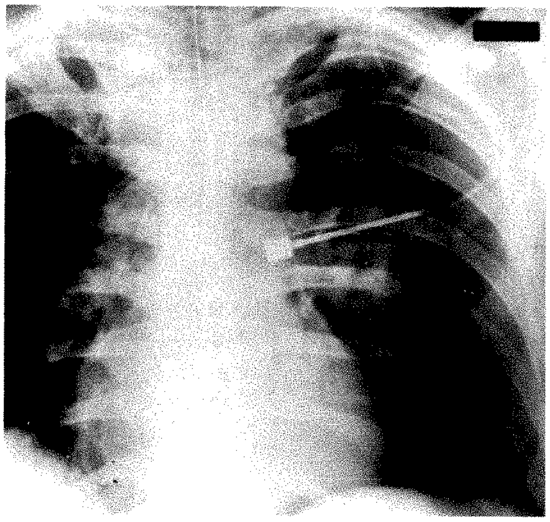

Fig. 7. Large left pneumothorax with total collapse of the left lung following placement of a left subclavian catheter. Although the catheter was functioning well, several attempts had been required before satisfactory placement was achieved. The pneumothorax was not suspected clinically at the time the roentgenogram was obtained.

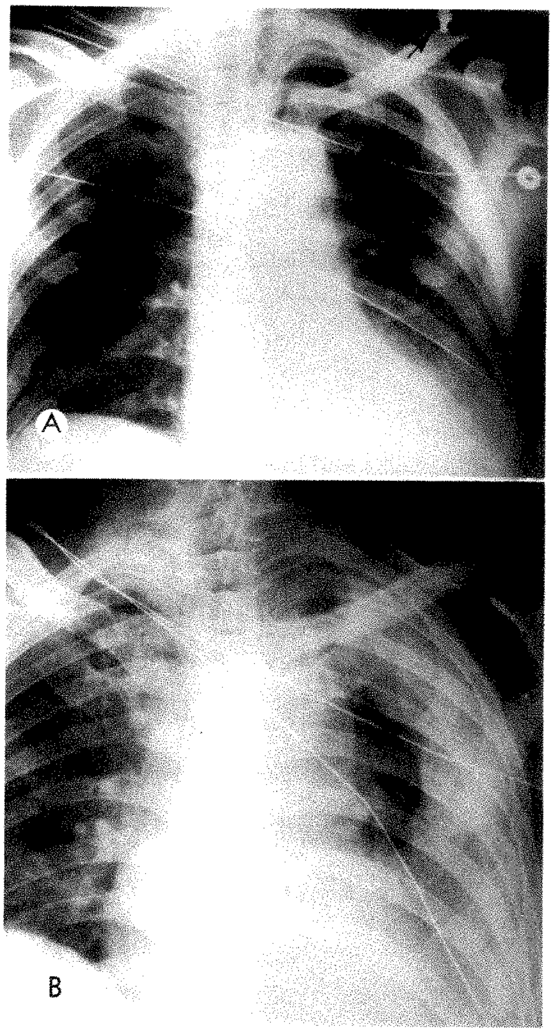

Fig. 8. (*A*) Initial chest roentgenogram obtained following placement of a left subclavian catheter. Only the metallic hub (arrow) of the catheter can be seen roentgenographically in this case, as the catheter itself is not radiopaque. There is a moderate sized left pleural effusion noted. (*B*) Follow-up examination one day later shows increasing left pleural effusion. Diagnostic considerations included major traumatic injury *vs.* ectopic infusion through the subclavian line which was not working well, and had been removed shortly before this film was obtained. A thoracentesis demonstrated that the pleural fluid was identical with the fluid which had been infused through the subclavian line.

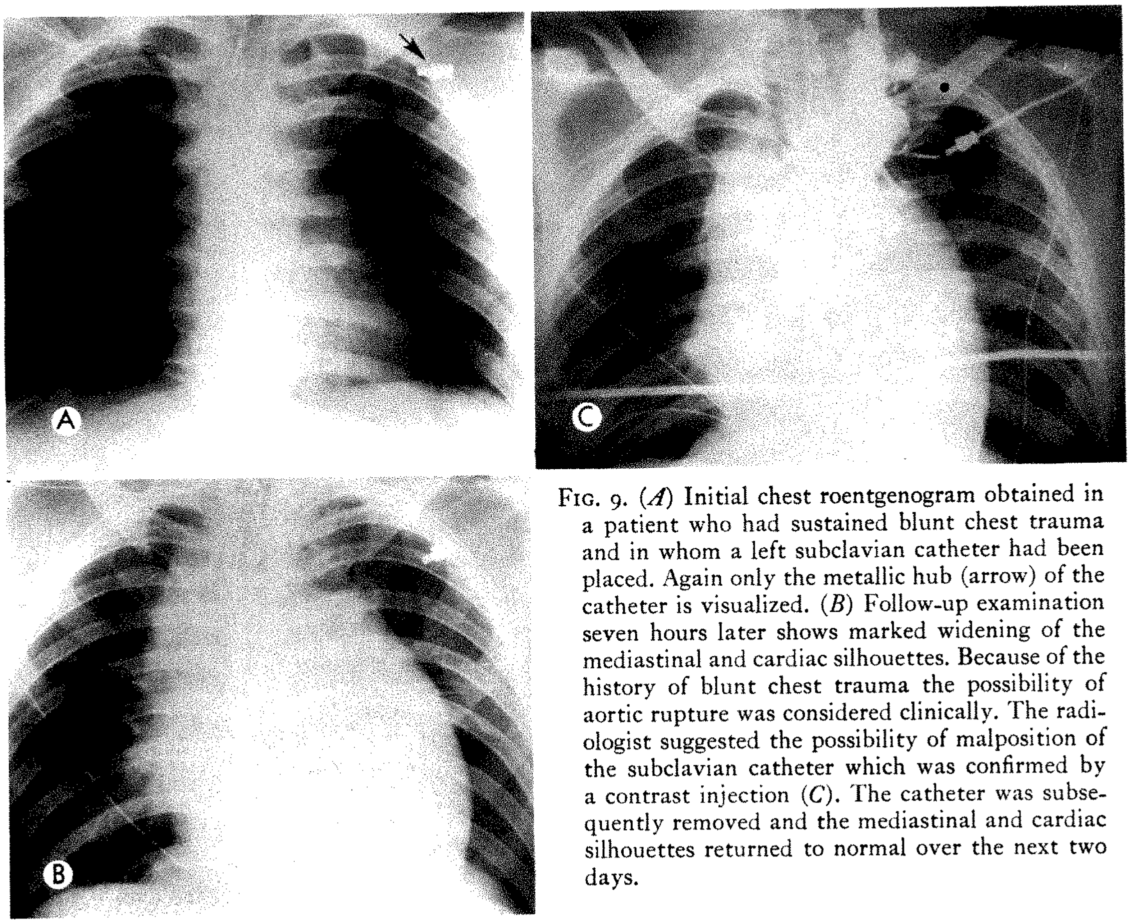

Fig. 9. (*A*) Initial chest roentgenogram obtained in a patient who had sustained blunt chest trauma and in whom a left subclavian catheter had been placed. Again only the metallic hub (arrow) of the catheter is visualized. (*B*) Follow-up examination seven hours later shows marked widening of the mediastinal and cardiac silhouettes. Because of the history of blunt chest trauma the possibility of aortic rupture was considered clinically. The radiologist suggested the possibility of malposition of the subclavian catheter which was confirmed by a contrast injection (*C*). The catheter was subsequently removed and the mediastinal and cardiac silhouettes returned to normal over the next two days.

in any patient in whom placement of the subclavian catheter has been attempted and has been unsuccessful, particularly before any attempt is made at placement on the opposite side.

The radiologist must consider the possibility of incorrect placement of a subclavian venous catheter whenever encountering significant pleural (Fig. 8) or mediastinal fluid (Fig. 9) in a patient in whom this procedure has been performed. Failure to suggest this diagnostic possibility can result in the incorrect consideration of a ruptured aorta or other major traumatic injury.

CENTRAL VENOUS PRESSURE CATHETERS

Prospective studies have shown that approximately one-third of central venous pressure catheters will be incorrectly positioned at the time of initial evaluation.[14] This results in inaccurate venous pressure measurements as well as ectopic infusion of potentially toxic solutions. The most common incorrect locations (Fig. 10) are the internal jugular vein, the hepatic veins and the subclavian vein distal to the venous valves. These valves are found in the subclavian vein and the internal jugular vein approximately 2.5 cm from their junction to form the innominate vein. Placement of the catheter distal to the valve results in an incorrect pressure measurement which can vary widely from the true central venous pressure. There is no consistent error but the measurements are usually elevated.[14]

INTRA-AORTIC BALLOON

The intra-aortic balloon has gained increasing popularity for use in conditions characterized by low output cardiac failure. It provides augmentation of diastolic coronary artery perfusion as well as reduced impedance to ventricular ejection.[2] Reported complications resulting from use of this device include: damage to the aorta, such as dissection of the aortic wall, laceration of the wall, and subadventitial hematoma; red blood cell destruction; embolic phenomena; vascular insufficiency of the catheterized limb; and balloon rupture with secondary gas embolism.[20] The most common complication observed by the radiolo-

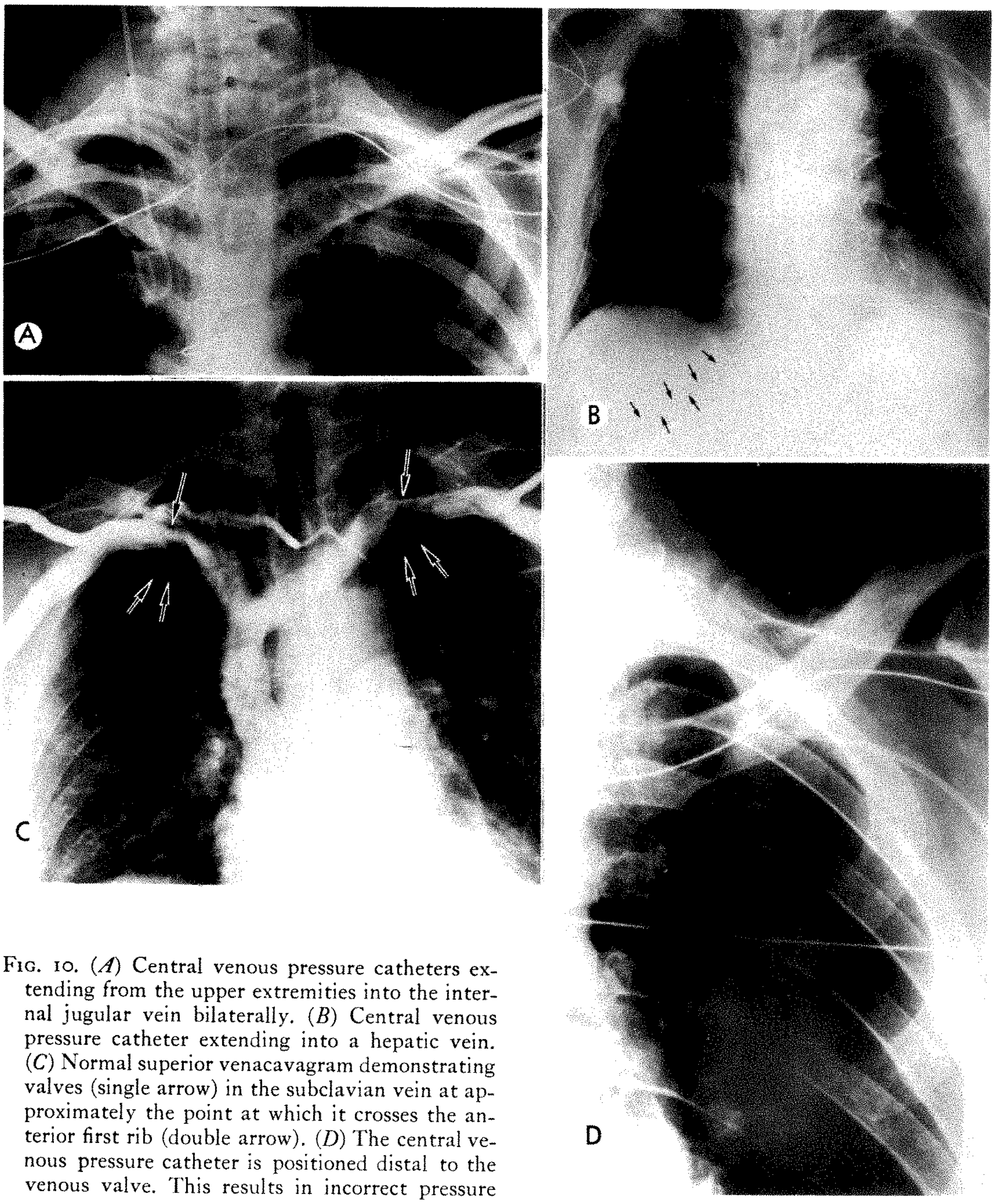

Fig. 10. (*A*) Central venous pressure catheters extending from the upper extremities into the internal jugular vein bilaterally. (*B*) Central venous pressure catheter extending into a hepatic vein. (*C*) Normal superior venacavagram demonstrating valves (single arrow) in the subclavian vein at approximately the point at which it crosses the anterior first rib (double arrow). (*D*) The central venous pressure catheter is positioned distal to the venous valve. This results in incorrect pressure measurements.

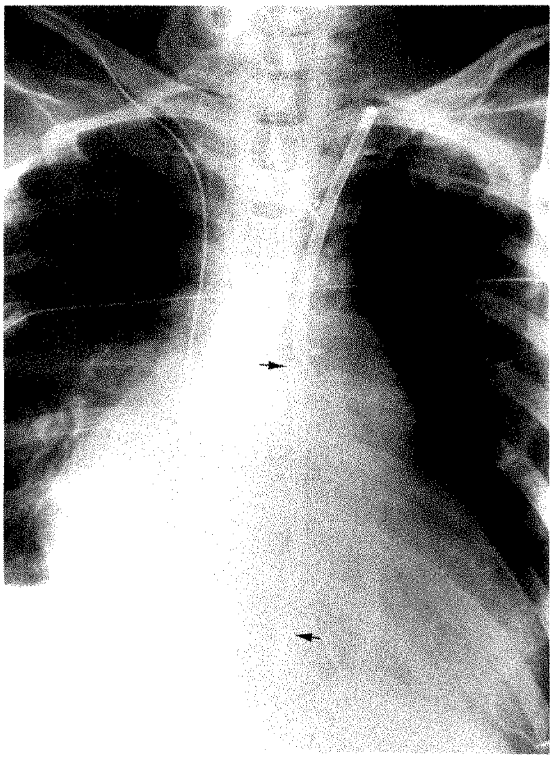

FIG. 11. Intra-aortic balloon (arrows) inadvertently positioned with its distal tip in the left subclavian artery.

gist, however, is improper positioning. The ideal position is to have the tip of the intra-aortic balloon just distal to the left subclavian artery. A position more proximal can occlude the left subclavian artery (Fig. 11) or result in emboli to the cerebral vessels. Distal positions result in decreased effectiveness of diastolic counterpulsation, and if too distal, can partially occlude the renal arteries.

CONCLUSION

Although great strides have been made in care of the critically ill patient over the past several decades, the life support and physiologic monitoring devices introduced to aid in patient management are not without hazards of their own. Many of the potential complications related to these devices have been reviewed in this paper. The radiologist, armed with an awareness of these complications, is in the unique position of being able to identify and to correct them before they become either clinically evident or adversely affect the patient's hospital course.

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A DEVICE TO MEASURE ROENTGENOGRAPHIC STRUCTURES*

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ABSTRACT:

A simple device and a nomogram are presented to permit rapid, accurate measurement of structures shown on roentgenograms. The arrangement is designed specifically for measurement of coronary vessels, but it can be adapted to other structures.

IN the presence of coronary artery disease, the calculation of quantitative degree of stenosis and the measurement of the diameter of the distal vessel provides values which are important for selecting candidates for coronary artery bypass surgery.[3,5] Accurate measurements should be obtained and corrected for distortion and magnification. However, making such measurements and corrections can be tedious and boring.

This study describes a simple device which allows convenient, rapid, and direct measurement of the true size of a coronary artery or any other roentgenographic structure from cut film or cine coronary arteriographs.

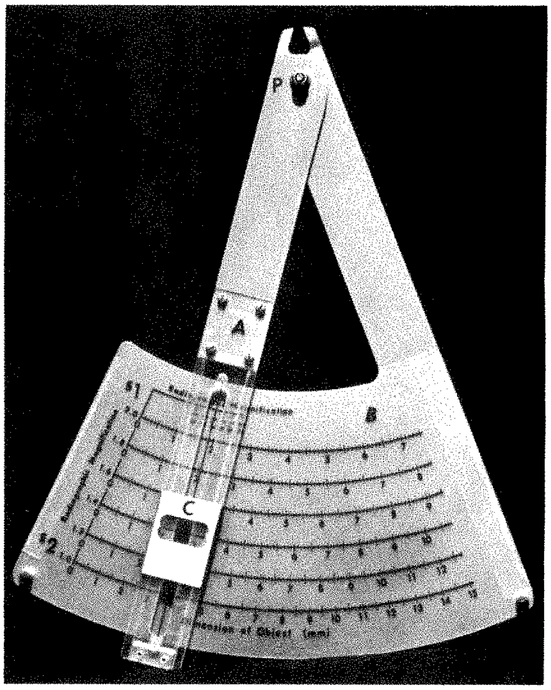

FIG. 1. The instrument is composed of a body (B) and a moveable arm (A) on which a cursor (C) slides. The body and moveable arm are joined at a pivot (P). The body bears two sets of scales, S1 and S2. The first set of scales (S1) bears numbers from 1.0 to 2.0: 1.0 represents no magnification, and 2.0 represents 100 percent magnification. This scale is used to measure the value of the roentgenographic magnification factor. The second set of six scales (S2) indicates the dimensions of the roentgenographic structure, in mm.

METHOD

Figure 1 shows the caliper. The ratio of the length of the arms on both sides of the pivot is approximately 10:1. The movable arm (A) carries a cursor with a window and a hair line. The body carries two sets of scales. The small scale (S1) is used to measure the size of the catheter on the roentgenogram, thus allowing determination of the magnification factor in the range of 1.0 to 2.0. Once the magnification factor is determined, the cursor is moved to frame the corresponding scale of the set (S2). This scale allows direct reading of the true size of all structures which are in approximately the same plane as the catheter. The scales are graduated for use with a French No. 8 catheter, but a similar caliper could be made for a catheter of larger or smaller size. The use of the caliper is simple and is

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rapidly learned by residents and fellows.

The accuracy of the measurements was determined by measuring a typical roentgenographic structure on the angiogram with a conventional metric scale. The value of the mean and the standard deviation of ten measurements was 4.0±0.1 mm. The same structure measured ten times with the caliper showed a standard deviation of 4.12±0.01 mm. Thus, the precision of the instrument was of an order of magnitude better than the precision of the standard

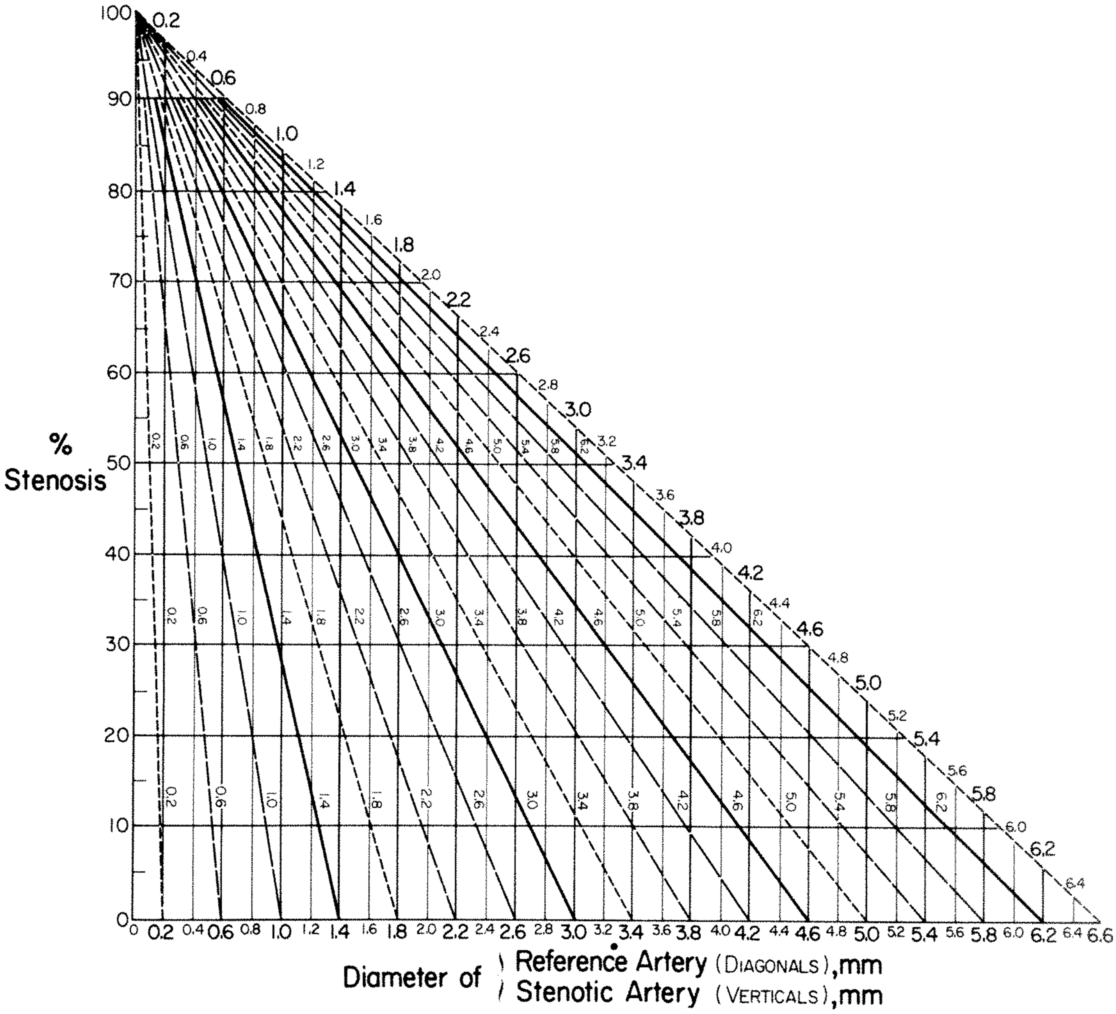

Fig. 2. Nomogram to convert measurements to percent stenosis. (1) Locate the diagonal line corresponding to the diameter of the artery. (2) Locate the perpendicular line corresponding to the diameter of the stenosis. (3) Find the intersection of the diagonal and the perpendicular lines. (4) Move from the point of intersection horizontally to the left. (5) Read the "percent stenosis" from the graduated vertical axis.

Example: Given: Diameter of artery = 5 mm
Diameter of stenosis = 1 mm
Find: Percent stenosis
Solution:
1. Find the diagonal line labeled 5.0
2. Find the vertical line labeled 1.0
3. Find the intersection of the diagonal and perpendicular lines
4. Move horizontally left and read "80 percent stenosis." A piece of paper has perpendicular edges. If the upper right corner is placed at the point, then the percent stenosis is easily read from the intersection of the upper edge of the paper and the vertical axis.

metric ruler. This higher precision is due to the 10:1 magnification obtained by the ratio of the length of the arms of the caliper. This magnification results in increased precision of reading the scales.

Figure 2 helps to convert the measurements made using the caliper to the percent stenosis. The horizontal, vertical, and diagonal lines are labeled with numbers. These lines are used together in the following way:

1. Locate the diagonal line labeled with the diameter (mm) of the nonstenosed portion of the artery of interest.
2. Locate the perpendicular line labeled with the diameter of the stenosis.
3. Find the intersection of these two diagonal and perpendicular lines.
4. Move from the point of intersection horizontally to the left axis.
5. Read the percent stenosis from the intersection with the graduated left axis.

These steps may be clarified by an example. Given, that the diameter of the artery is 5 mm and that the diameter of the stenosis is 1 mm, the solution proceeds by way of the following steps:

1. The diagonal line labeled 5.0 is located.
2. The vertical line labeled 1.0 is found.
3. The intersection of these diagonal and vertical lines is located.
4. One moves horizontally left from the intersection to the vertical axis, where "80 percent" stenosis is read.

A piece of paper has perpendicular edges. If the upper right corner is placed at the point of intersection of the diagonal and vertical lines, then the percent stenosis is conveniently read from the intersection of the upper edge of the paper and the vertical axis.

DISCUSSION

A previous study[6] described a method for measuring the diameter of the coronary artery using tables. Since the original article was published, we have found it necessary to expand the original table twice in order to use the method for larger structures or for a stenosis of greater length. Although the extended table is useful, it became apparent that a more flexible tool was needed than either a table or a graph. Furthermore, this would permit the angiographer to measure a variety of structures directly. (Table 1 shows the extended table.)

In order to obtain correct measurements, it is of paramount importance to measure only areas which are approximately in the same plane with the catheter. The size of the catheter itself should be measured as follows:

Left posterior oblique or right anterior oblique projections: left anterior descending artery and posterior descending artery can be measured over their entire length.

Left anterior oblique projection: In this projection, the atrioventricular groove lies in the same plane as the catheter; therefore, the right coronary artery, the left main coronary artery, and the circumflex can be measured throughout their length. This projection would not lend itself to accurate measurement of the left anterior descending artery, diagonal branches, especially their mid and distal portions, the posterior descending artery, especially not towards the apex. The marginal branches of either the right coronary artery or the marginal branches of the circumflex should not be measured in this projection; they will be minified in the left anterior oblique projection, but they will be magnified in the right posterior oblique projection.

Lateral: This projection is seldom used for measurements. However, it would still be acceptable for both the left anterior descending artery and the posterior descending artery.

Any projection can be used for the most proximal portion of the catheterized vessel because it is close to the catheter. Therefore, the right coronary artery ostium and the left coronary artery ostium can be mea-

Table I*

DETERMINATION OF THE DIAMETER OF CORONARY ARTERIES: THESE VALUES APPLY FOR A NO. 8 FRENCH CATHETER (2.7 MM O.D.)

Magnification Factor	1.11	1.30	1.48	1.67	1.85	2.04	2.22
	Y, mm Diameter of Image of Catheter						
Artery Image X mm	3.0	3.5	4.0	4.5	5.0	5.5	6.0
.5	.5	.4	.3	.3	.3	.2	.2
1.0	.9	.8	.7	.6	.5	.5	.5
1.5	1.4	1.2	1.0	.9	.8	.7	.7
2.0	1.8	1.5	1.4	1.2	1.1	1.0	.9
2.5	2.3	1.9	1.7	1.5	1.4	1.2	1.1
3.0	2.7	2.3	2.0	1.8	1.6	1.5	1.4
3.5	3.2	2.7	2.4	2.1	1.9	1.7	1.6
4.0	3.6	3.1	2.7	2.4	2.2	2.0	1.8
4.5	4.1	3.5	3.0	2.7	2.4	2.2	2.0
5.0	4.5	3.9	3.4	3.0	2.7	2.5	2.3
5.5	5.0	4.2	3.7	3.3	3.0	2.7	2.5
6.0	5.4	4.6	4.0	3.6	3.2	2.9	2.7
6.5	5.9	5.0	4.4	3.9	3.5	3.2	2.9
7.0	6.3	5.4	4.7	4.2	3.8	3.4	3.2
7.5	6.8	5.8	5.1	4.5	4.1	3.7	3.4
8.0	7.2	6.2	5.4	4.8	4.3	3.9	3.6
8.5	7.7	6.6	5.7	5.1	4.6	4.2	3.8
9.0	8.1	6.9	6.1	5.4	4.9	4.4	4.1
9.5	8.6	7.3	6.4	5.7	5.1	4.7	4.3
10.0	9.0	7.7	6.8	6.0	5.4	4.9	4.5
10.5	9.5	8.1	7.1	6.3	5.7	5.2	4.7
11.0	9.9	8.5	7.4	6.6	5.9	5.4	5.0
11.5	10.4	8.9	7.8	6.9	6.2	5.6	5.2
12.0	10.8	9.3	8.1	7.2	6.5	5.9	5.4
12.5	11.3	9.6	8.4	7.5	6.8	6.1	5.6
13.0	11.7	10.0	8.8	7.8	7.0	6.4	5.9
13.5	12.2	10.4	9.1	8.1	7.3	6.6	6.1
14.0	12.6	10.8	9.4	8.4	7.6	6.9	6.3
14.5	13.1	11.2	9.8	8.7	7.8	7.1	6.5
15.0	13.5	11.6	10.1	9.0	8.1	7.4	6.8
15.5	14.0	12.0	10.5	9.3	8.4	7.6	7.0
16.0	14.4	12.3	10.8	9.6	8.6	7.9	7.2
16.5	14.9	12.7	11.1	9.9	8.9	8.1	7.4
17.0	15.3	13.1	11.5	10.2	9.2	8.3	7.7
17.5	15.8	13.5	11.8	10.5	9.4	8.6	7.9
18.0	16.2	13.9	12.1	10.8	9.7	8.8	8.1
18.5	16.7	14.3	12.5	11.1	10.0	9.1	8.3
19.0	17.1	14.7	12.8	11.4	10.3	9.3	8.6
19.5	17.6	15.0	13.2	11.7	10.5	9.6	8.8
20.0	18.0	15.4	13.5	12.0	10.8	9.8	9.0
20.5	18.5	15.8	13.8	12.3	11.1	10.1	9.2
21.0	18.9	16.2	14.2	12.6	11.3	10.3	9.5
21.5	19.4	16.6	14.5	12.9	11.6	10.6	9.7
22.0	19.8	17.0	14.9	13.2	11.9	10.8	9.9
22.5	20.3	17.4	15.2	13.5	12.2	11.0	10.1

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* The size of the diameter of the image of the coronary artery, X, and the diameter of the image of the catheter, Y, are measured on the roentgenogram. If the true diameter of the catheter is 2.7 mm, then X and Y are used to locate the true diameter Z, of the coronary artery in the table, $Z = 2.7(X/Y)$. Z is the true diameter of the artery at that point, (mm). X is the outside diameter of the artery, as measured on the film (mm). Y is the outside diameter of the image of the catheter, as measured on the film (mm).

Table I—(*Continued*)

Magnification Factor	1.11	1.30	1.48	1.67	1.85	2.04	2.22
	Y, mm Diameter of Image of Catheter						
Artery Image X mm	3.0	3.5	4.0	4.5	5.0	5.5	6.0
23.0	20.7	17.7	15.5	13.8	12.4	11.3	10.4
23.5	21.2	18.1	15.9	14.1	12.7	11.5	10.6
24.0	21.6	18.5	16.2	14.4	13.0	11.8	10.8
24.5	22.1	18.9	16.5	14.7	13.2	12.0	11.0
25.0	22.5	19.3	16.9	15.0	13.5	12.3	11.3
25.5	23.0	19.7	17.2	15.3	13.8	12.5	11.5
26.0	23.4	20.1	17.5	15.6	14.0	12.8	11.7
26.5	23.9	20.4	17.9	15.9	14.3	13.0	11.9
27.0	24.3	20.8	18.2	16.2	14.6	13.3	12.2
27.5	24.8	21.2	18.6	16.5	14.9	13.5	12.4
28.0	25.2	21.6	18.9	16.8	15.1	13.7	12.6
28.5	25.7	22.0	19.2	17.1	15.4	14.0	12.8
29.0	26.1	22.4	19.6	17.4	15.7	14.2	13.1
29.5	26.6	22.8	19.9	17.7	15.9	14.5	13.3
38.8	27.0	23.1	20.3	18.0	16.2	14.7	13.5

sured in any plane because of their proximity to the catheter.

Areas of stenosis should be measured in whichever projection they appear the most marked. Once the diameter of the stenosis has been obtained, comparison with the most proximal area of normal-appearing vessel can be made in order to measure the degree of stenosis. Figure 2 can be used to determine the percent of stenosis.

All measurements of relative coronary artery stenosis or of absolute coronary artery size are subject to criticism,[1] particularly if angiographic and anatomical findings are compared.

Vlodaver *et al.*[7,8] compared 134 segments of coronary arteries angiographically and pathologically in ten cases. Thirty-three percent of the segments had a false negative arteriographic diagnosis of obstructing plaques, 64 percent of the segments were in agreement, and in 3.5 percent a false positive angiographic diagnosis was made. Vlodaver listed five major factors underlying these discrepancies: (1) inadequate roentgenographic technique; (2) lack of visualization of lesions in profile due to limited projection; (3) slit-like lumen adjacent to an atheroma; (4) comparison of more severely obstructed segments with less severely diseased segments at the time of angiography; and (5) misinterpretation of obstructing lesions at the time of postmortem study.

There is no question that significant and even severe stenosis can be overlooked on inadequate angiograms. Ideally, more than four projections should be obtained during coronary angiography. An improved demonstration of arteries, particularly at the origin of the left anterior descending and circumflex, has been achieved by angle views proposed by Lespérance *et al.*[4] The other main reason for this discrepancy between angiography and postmortem findings is explained by the lack of distention of the arteries at the postmortem examination. Furthermore, the pathologic measurements compared the diameter of the lumen to the outside diameter of the artery; and the angiographic measurements referred only to luminal changes. Therefore, it is conceivable that a 20 percent stenosis determined at the time of angiography may become a 3+ stenosis as seen in the pathologic specimen.

Another study comparing pre- and postmortem material is by Grondin *et al.*[2] who presented 23 cases. Of a total of 145 angiographically significant lesions of the coronary arteries in the pathologic specimens, only eleven lesions (7.5 percent) proved at autopsy to have been grossly underestimated at angiography. Grondin also pointed out that, in general, the arterial lesions appeared more severe and more extensive or diffuse at postmortem examination than at angiography. However, Grondin also insists that the quality of the angiogram plays an important role.

Rösch *et al.*[5] reported another excellent study comparing the size of the coronary arteries measured from angiograms and measured *in vivo* during surgery. Of 253 surgically explored arteries, preoperative angiographic appraisal of the distal vessels was accurate in 219 (86 percent) and inaccurate in 34 (14 percent). An accuracy of 97 percent was obtained if measurements were applied to poststenotic vessels which filled antegradely. The accuracy was lower (76 percent) beyond occlusions with retrograde collateral flows. The accuracy was 65 percent in vessels beyond occlusions filled by insufficient collaterals.

Lespérance *et al.*[3] have shown that the patency rate of coronary bypass grafts is much higher if the anastomosed artery has a diameter of 1.5 mm or more. Consequently, it is our belief that careful measurement of the poststenotic segment of the coronary artery can help predict if the coronary bypass graft will remain patent.

CONCLUSION AND SUMMARY

A simple instrument is described which allows convenient and rapid determination of true coronary artery size from cut film and cine coronary arteriograms. Measurements made using this instrument proved to be more precise than the use of a standard metric ruler. The size of the catheter is measured on the angiogram, and the magnification factor is determined. True arterial size can be directly read on the corresponding scale.

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ANNUAL MEETING: September 20–24, 1976, Washington, D. C., Washington Hilton Hotel.

SCIENTIFIC PROGRAM: Seymour Ochsner, *President Elect*, Ochsner Clinic, New Orleans, La.

MANAGER ANNUAL MEETING: George A. Kling, Harper Hospital, Detroit, Mich.

MEMBERSHIP: Hymer Friedell, Chairman, Executive Council,
Case Western Reserve University, Cleveland, Ohio 44106.

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Representative on the Board of Chancellors of the American College of Radiology: J. A. del Regato.

Liaison Representative on the National Council on Radiation Protection and Measurements: Lawrence W. Davis.

ANNUAL MEETING: May 9–14, 1976, Vancouver, British Columbia, Bayshore Inn.

SCIENTIFIC PROGRAM: Felix N. Rutledge, *President*, Houston, Texas

LOCAL ARRANGEMENTS: John M. W. Gibson, Vancouver, British Columbia

MEMBERSHIP: Richard H. Jesse, *Secretary*, M. D. Anderson Hospital and Tumor Institute,
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EDITORIAL

THE JAMES PICKER FOUNDATION FOR RADIOLOGIC RESEARCH

For 25 years the James Picker Foundation has provided grant support for radiologic research and training, yet this unique institution has not been widely publicized and its purposes and achievements are unfamiliar to many. A brief review of its history and current program may be of interest.

The foundation was conceived by James Picker "to assist, promote, and encourage the study and development of the science of radiology, roentgen ray research, and related sciences, so that the general welfare might be enhanced in their medical application." The first Board of Directors was appointed in 1949 and, with the exception of Ross Golden (then professor and chairman of radiology at Columbia University), was made up of distinguished laymen. Harold E. Stassen was its first president.

At that time radiology had not been accorded the status of a major medical discipline, although some notable technical and medical advances were occurring. To strengthen radiology's position in the scientific community and to obtain expert scientific advice for its program, the board enlisted the assistance of the National Academy of Science–National Research Council. The NAS/NRC Committee on Radiology was established and chaired first by Eugene P. Pendergrass. The committee advised the board and carried out the foundation program from 1950 to 1974, developing awards, reviewing applications, and making recommendations and appropriations. The early program included grants in aid for research projects and fellowships, primarily in radiation biology and physics. In recent years worthy clinical projects of immediate medical significance have been recognized and received support.

Some of the nation's most talented scientists and physicians have served on the Committee on Radiology, guiding the program as radiology has evolved in the past quarter century. During the same period the composition of the Board of Directors gradually changed from laymen to medical scientists. As a consequence of this and because of increasing costs of the services provided by the NAS/NRC, the foundation terminated its long and productive association with the NAS/NRC in 1974 and began to manage its program directly through its Board of Directors.

Since its inception, the foundation program has been characterized by generosity, growth, and variation. It has been repeatedly reviewed and modified to best meet changing needs. But throughout, emphasis on support for individuals rather than support for specific projects or short-term objectives has been a dominant feature. In his initial discussions with the NAS/NRC, Picker expressed the hope of providing as much as \$30,000–\$40,000 a year for the program. As of this writing, 25 years later, approximately \$10,000,000 has been disbursed in more than 430 grants: 204 have been research grants and 142 were commitments to individuals for academic training. Eighty-four medical students have been subsidized for short periods of study. The foundation has also assisted with special projects such as preparation of the multivolume *Atlas of Tumor Radiology* and the in-depth study entitled *Survey of Academic Radiology*. In recent years special noncategorical awards to Meharry and Howard Universities and the Drew Postgraduate Medical School have advanced radiology programs at these minority group educational institutions.

Over the years Research Fellowships, Scholar Grants, Advanced Academic Fellowships, and James Picker Fellowships have been awarded to a variety of young scientists interested in furthering their training in clinical investigation or acquiring special educational skills and basic science techniques. As of 1970, 67 of the 83 United States university graduates so supported continued as members of faculties in radiology in this country; 13 are currently department chairmen. While the foundation cannot take exclusive credit for shaping the careers of these individuals, doubtless the path was made easier by the Picker grants.

The foundation continues to emphasize individual support, although small grants for pilot research projects are available. The present award, the James Picker Scholarship, is similar to the John and Mary Markle Scholarship which supported promising academicians, many of whom have become today's academic leaders. The James Picker Scholarship makes a 4 year commitment to approximately 10 young faculty members yearly. Funds totaling $40,000 over the 4 year period are granted for use as the sponsoring institution and the candidate conceive to be optimum for his/her particular goals. In certain cases a year or more of full support can be provided for special training outside of the candidate's institution. Such opportunities for advanced training have become all the more precious with the virtual termination of federal support for research training in favor of goal-oriented investigation.

The current Picker program emphasizes the imaging fields, diagnostic radiology, nuclear medicine, diagnostic ultrasound, and the sciences fundamental to image technology. Other branches of radiology oriented toward cancer biology and therapy continue to be in a more favorable position for support from federal programs. Although they are not currently assisted by the foundation, their needs in the future may require program reorientation.

Applications for the James Picker Scholarship are solicited in early October from approved schools of medicine on behalf of designated young faculty candidates. Candidates are interviewed and selected in January for award the following July. Eligibility does not require employment in a university hospital. The candidate may work in other institutions, his eligibility being established by his faculty appointment and a close affiliation between his institution and the medical school.

Thus through the generosity and vision of James Picker, an endowment exists for the advancement of radiology as a medical science. The foundation has been notably successful in working toward this goal. However, it is the editor's impression that our medical specialty has been insufficiently aware of this unique resource, the faith that inspired it, and the wisdom that has directed it. The James Picker Foundation is one of radiology's special assets, a generous gift enabling radiology to more effectively serve medicine and mankind through research and research training. May it endure and prosper.

MMF

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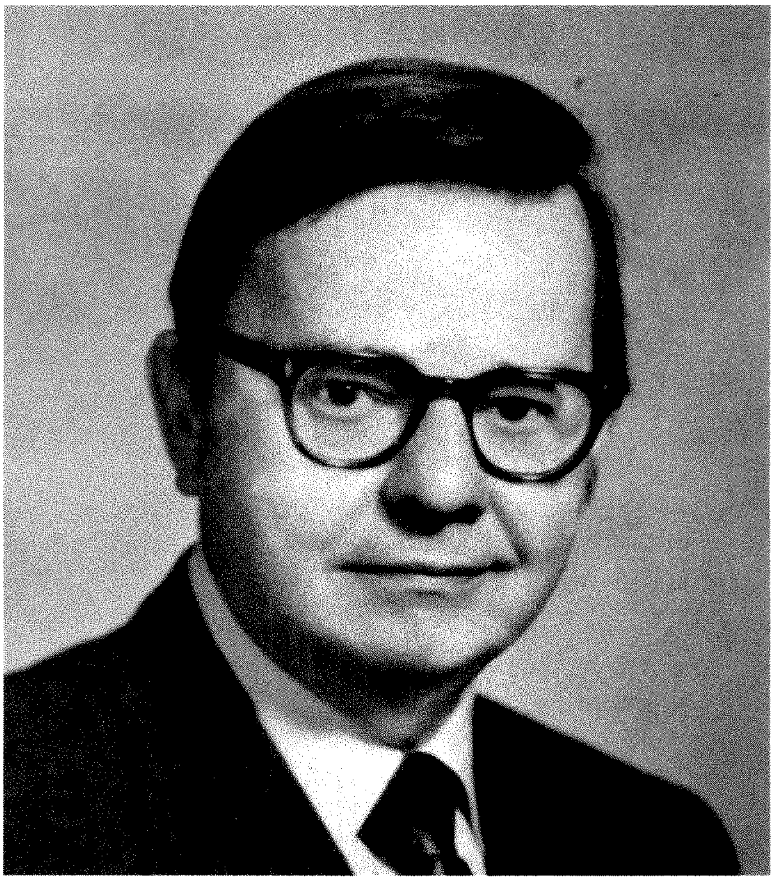
IN MEMORIAM



FERNANDO G. BLOEDORN, M.D.
1913–1975

FERNANDO G. BLOEDORN was born in Brazil on October 12, 1913. Shortly afterwards his family moved to Rosario, Argentina, where he obtained his Medical Degree from the University del Litoral at 23 years of age. For 14 years, he practiced general surgery in a small town. A man of his intellect and drive would, of course, not remain satisfied in a prosperous surgical practice. Following the advice of his Professor of Surgery, he decided to learn about cancer. Initially at his own expense, Fernando went to Milan to study at the Istituto del Cancro, now the Istituto Nazionale Tumori. Of most interest was the radiation treatment of cancer, primarily radium therapy. He next went to the Curie Fondation in Paris and then, on a British Council

Scholarship, he spent 18 months at the Christie Hospital in Manchester. There he learned the fundamental techniques and dosimetry of interstitial and intracavitary radium therapy as well as the dosimetry of external beam therapy. He came to the United States of America in January 1951 as Senior Resident in Radiotherapy at the Frances Delafield Hospital.

I met Fernando in the summer of 1951 during one of my visits to that Institution. We had much in common, both having an interest in developing Radiotherapy to be a major tool in the management of cancers. We shared the conviction that Radiotherapy should play the important role which it had in England and the Scandinavian countries but, for historical reasons, had not developed in the United States. Fernando joined me at the M. D. Anderson Hospital and stayed from the fall of 1951 to August 1955. He was an immense help in those years of rapid expansion of the clinical material.

In the early part of 1955, Fernando felt, with his drive, the need to leave the nest and to develop his own place. He started as an Associate Professor of Radiology at the Maryland School of Medicine in September 1955. There was only an old 200 Kv unit for the few patients treated. Within two years, a ^{60}Co unit and a 35 MeV Brown-Boveri betatron were installed in a brand new building. Within five years, there were two ^{60}Co units and more than 1,000 new patients per year being treated at the University Hospital. In addition to building this sizable Department, he was unique in establishing a number of "substations" in the State of Maryland to treat cancer of the cervix in collaboration with the local Gynecologists. The results of this cooperative effort have been published and show that one can, with cooperation, effectively use modern Radiotherapy and obtain outstanding cure rates for cervical cancer.

Although a new Department had been built, space became increasingly limited, especially for research expansion. Fernando realized that he could not adequately develop his full potential for organization unless he had a separate Department of Radiation Therapy rather than a Division of Radiation Therapy in a Department of Radiology. In 1968, age 55 years, he moved to the New England Medical Center and Tufts Medical School where, until his death, he was Professor and Chairman of the Department of Therapeutic Radiology. The only equipment available when he arrived was a 2 MeV Van de Graaff located at the Lemuel Shattuck Hospital, a state-owned hospital affiliated with Tufts Medical School.

Immediately, Fernando started to develop a new Department in the basement of the New England Medical Center. Within two years, through various sources of funding, an automated ^{60}Co unit and a 45 MeV Brown-Boveri betatron were installed. A second phase of expansion for research facilities was supported in part by a National Cancer Institute grant. By 1975, less than six years from the day Fernando had arrived, the Department occupied 21,800 square feet, half of this being space for research laboratories. The Staff consists of 85 members, 35 of them being professionals at the M.D., or Ph.D. level. There are extensive computer facilities and a room designed to hold a neutron beam generator. The number of new patients treated annually under Fernando's supervision, including the affiliated hospitals, was 1,050 by 1971–1972 and exceeded 1,600 in 1974–1975. The current number of Residents and Fellows is 16.

Of the many honors Fernando received and the numerous memberships in societies he held, he cherished most to have been President of the American Radium Society. What appealed to him particularly in this society was the multidisciplinary membership. This appeal had its roots in having himself practiced surgery for many years before becoming a Radiotherapist. During his seven years on the Executive Committee of the American Radium Society, he pushed relentlessly the recruitment of surgical members.

Fernando is one of the Founders of modern Radiotherapy in the United States. Fernando was a superb "Needler" and master clinician, just as he must have been skillful as a Surgeon. He performed irradiation treatments with the same meticulous care that the Surgeon uses when he performs an operation.

Fernando made significant contributions in the utilization of radiotherapy alone but his main contribution has been his abiding interest in combining irradiation and surgery. He grasped the value of this approach very early. As a former Surgeon, he was keenly aware of the inability of surgery to always eradicate all cancer cells and as a Radiotherapist, he was also aware of the difficulty of curing gross cancer with irradiation.

Although Fernando had little background in research he recognized its value and potential. Perhaps his greatest asset was a clarity of mind which aided him in hiring outstanding people in basic research. Having served twice on the Radiation Study Section of the National Institutes of Health, he had acquired an in-depth perspective for the significance of Radiation Research in cancer therapy and for recognizing the creative researchers.

Fernando is survived by his wife, Nellie, a companion who has followed him through his many travels and changes of locations, each time creating a relaxed and elegant home. As their houseguest on innumerable occasions, I thoroughly enjoyed Nellie's home and excellent cooking.

Modern Radiotherapy has lost one of its Founders and I have lost my closest friend. Fernando was a sharp evaluator of human affairs and one could not pull the wool over his eyes. His tongue could be caustic but usually was tempered by a keen sense of humor. I will miss our many long hours of walks during which we talked about the past, present, and future of Radiotherapy and Oncology. One of the joys of conversing with Fernando was to hear his gaucho proverbs reflecting the life wisdom of the Spanish culture which makes Don Quixote a most relaxing reading in times of stress. It is hard for me to accept that I will not hear anymore, "As the gaucho says. . . . "

GILBERT H. FLETCHER, M.D.

CHARLES HANSON PETERSON, M.D.
1904–1975

CHARLES HANSON PETERSON, M.D. died at his home, Route 1, Hollins, Virginia on Monday, November 10, 1975 after a long illness. Born in Monterey, Highland County, Virginia, January 25, 1904, he attended the University of Virginia for undergraduate work and graduated from the School of Medicine of the University of Virginia in 1926. He served as intern, resident in medicine and resident in radiology, all at the University of Virginia Hospital.

In 1930 Dr. Peterson moved to Roanoke, Virginia where he became Radiologist to the Jefferson Hospital and remained in that position until the Jefferson Hospital was merged with the Community Hospital of Roanoke Valley in 1967. He was Consulting Radiologist at the Community Hospital until his retirement in 1970. In 1931, Dr. Peterson opened an office in Roanoke for the private practice of radiology. He was joined in this office in 1938 by Dr. Allen Barker and in 1941 by Dr. Charles D. Smith to form the firm of Peterson, Barker and Smith. Following the addition of several other associates over a period of several years, the group became Radiology

Associates of Roanoke in 1966 with Dr. Peterson remaining as senior member until his retirement in 1970.

Dr. Peterson was a member and Deacon of the First Presbyterian Church of Roanoke and a member of the Roanoke Rotary Club.

He had been a member of the American Roentgen Ray Society since 1934. He was a diplomate of the American Board of Radiology, having received his certificate in 1934 in the first group of radiologists recognized by the ABR. He was a member of the Roanoke Academy of Medicine and was president of that organization in 1948. He was a member of the Virginia Radiological Society (Virginia Chapter-ACR) and was president of that organization in 1948. He was a member of the Southern Medical Association and was elected Chairman of the Section of Radiology of that society in 1941. In addition, he was a member of the AMA, The Medical Society of Virginia, the Radiological Society of North America, The American Radium Society and a Fellow of the American College of Radiology.

Dr. Peterson was the first formally trained radiologist in Southwest Virginia and was on the staff of the Shenandoah Hospital, the Lewis-Gale Hospital and the Roanoke Memorial Hospital, all of Roanoke. He was Consulting Radiologist to the Veterans Administration Hospital of Salem, Virginia.

He was a member of the U.S. Naval Reserve and was called to active duty shortly after Pearl Harbor. He was sent to Londenderry, North Ireland, and served in the U.S. Naval Hospital there from January 1942 until he was returned to Portsmouth, Virginia in June 1944. He was relieved of active duty in the Navy in November 1945 with the rank of Captain.

Dr. Peterson was married to Cornelia Brookings. They had three children: Charles H. Peterson, Jr., M.D., Roanoke, William B. Peterson, Martinsville, Virginia and Nancy Stuart Peterson, Hollins, Virginia, and four grandchildren.

As founder of a large radiology group, Dr. Peterson insisted on selection of associates to maintain high quality radiologic services. Once an associate was chosen, Dr. Peterson never interfered with his professional work, though he was always available for professional consultations, to discuss public relations and to discuss personal matters; in these relationships he had the happy faculty of expressing a solution to the matter in a droll and humorous way.

Dr. Peterson chose his possessions and friends carefully and believed he lived in the best of all worlds: in his opinion, he had the best family, the best house, the best professional associates and the best friends and those of us who were fortunate enough to know him and be associated with him are inclined to agree. He lived a full and happy life, accomplishing many things without fanfare. His presence is, and will be, sorely missed.

James G. Snead, M.D.
John A. Martin, M.D.
Charles D. Smith, M.D.

FIFTY-EIGHTH ANNUAL MEETING OF THE AMERICAN RADIUM SOCIETY

THE Bayshore Inn Hotel in Vancouver, British Columbia will be the site of the Fifty-eighth Annual Meeting of the American Radium Society to be held on May 9–13, 1976.

This is our first meeting in Vancouver, a city which excels in scenic beauty, mild climate and attractive people. The Bayshore Inn, the site of the meeting, is situated on the water's edge and provides a view of the bay with a beautiful mountain range in the background and the skyline of the city nearby. The Stanley Park, only a short distance away, can be viewed from the upper level of the hotel. The movement of boats and small sea planes immediately about the hotel makes a fascinating disturbance of the light reflection upon the beautiful bay water. For those who arise early, the ascent of the sun above the mountain range makes the early hours exciting. Several fine restaurants in the Bayshore Inn provide a view of the surrounding gardens which enhances enjoyment of the excellent cuisine.

Our Local Arrangements Committee Chairman, Dr. J. M. Gibson, has arranged our evening social program which will be similar to those for previous meetings, beginning with a reception for arriving guests on Sunday. An evening boat trip is planned for Monday, and the annual banquet will be served Wednesday evening. The style of the banquet will differ from the usual with a British pub theme and appropriate music and entertainment to replace speeches. Daytime tours of the Stanley Park and Queen Elizabeth Gardens, and a tour of the universities to see the extensive gardens and fine examples of modern architecture will provide entertainment for the ladies and the men who may steal away from the scientific program.

Flowers abound but those seen at the Butchart Gardens in Victoria on Vancouver Island will afford an experience long remembered. Enroute to Victoria the boat crosses beautiful waters from Vancouver and cruises among forested islands to a land favored for vacation living because of its natural beauty and mild climate. A visit to the Empress Hotel and afternoon tea is a highlight of the trip to Victoria. Ample time is allowed in Vancouver for non-programmed activities such as shopping and sailboating.

The scientific sessions will be held in the mornings, Monday through Thursday from 8:30 to 1:30. The program has been designed to present a balance of subjects from various specialties and to emphasize topics that have not been discussed at the Society meetings. Each day's program will begin with a panel of authorities who will introduce and discuss a topic for the first $1\frac{1}{2}$ hours. Proffered papers related to the panel topic will be presented, when possible, on the same day. The panel topics are: on Monday, Current Status of Immunology and Immunotherapy, organized by Dr. Alfred Ketcham; on Tuesday, Soft Tissue Sarcomas in Children, organized by Dr. Luther Brady; on Wednesday, Carcinoma of the Prostate, organized by Dr. Douglas Johnson; and on Thursday, Carcinoma of the Ovary, organized by Dr. Julian Smith.

The traditional Janeway Lecture will be delivered by Dr. Audrey Evans of the Children's Hospital, Philadelphia, Pennsylvania. The award winning paper submitted by a resident will be presented.

More than 34 proffered papers will be presented. These papers were selected by the Scientific Program Committee by review of a much larger number of abstracts.

As always, registration is open to all interested physicians. Advanced registration by mail is suggested to avoid congestion and delays. Registration forms and hotel reservation cards will be mailed to members of the American Radium Society. Other physicians may request this material from Dr. J. M. Gibson, British Columbia Cancer Institute, 2656 Heather Street, Vancouver, British Columbia, Canada. There is no fee for members. Nonmembers must pay a registration fee. A review of the topics for the scientific program and the planned social activities in beautiful British Columbia indicates that this will be an outstanding meeting. We are looking forward to greeting you in Vancouver.

Felix N. Rutledge, M.D.
President, American
Radium Society

THE AMERICAN RADIUM SOCIETY

FIFTY-EIGHTH ANNUAL MEETING

Bayshore Inn Hotel, Vancouver, British Columbia
May 9–13, 1976

PRELIMINARY PROGRAM

Sunday, May 9, 1976

9:00 A.M.–4:00 P.M. Executive Committee Meeting
9:00 A.M.–5:00 P.M. Registration
6:00 P.M.—Welcoming Reception

Monday, May 10, 1976

8:00 A.M.–8:30 A.M. Opening Ceremonies. President's Address. The Estrogen Risk. Felix Rutledge, M.D., Houston, Texas.

8:30 A.M.–1:15 P.M. First Scientific Session. *Presiding;* Jerome M. Vaeth, M.D., San Francisco, California

8:30 A.M.–10:00 A.M. *Symposium:* The Problems of Practical Application of Immunotherapy. *Moderator:* Alfred S. Ketcham, M.D., Miami, Florida. *Participants:* William Wara, M.D., University of California, San Francisco, California; Charles McKhann, M.D., University of Minnesota, Minneapolis, Minnesota; and Frederick Eilber, M.D., University of California at Los Angeles, Los Angeles, California.

10:00 A.M.–10:15 A.M. Intermission

10:15 A.M.–10:30 A.M. Cytochemical and Immunological Evaluations of Women Treated for Squamous Carcinoma of the Cervix. Z. L. Olkowski, M.D., J. R. McLaren, M.D. and S. A. Wilkins, Jr., M.D., Emory University Clinic, Atlanta, Georgia.

10:30 A.M.–10:45 A.M. Carcinoembryonic Antigens in Patients Undergoing Radiation for Invasive Carcinoma of the Uterine Cervix. J. R. van Nagell, Jr., M.D., E. Donaldson, M.D., D. M. Goldenberg, M.D. and Q. Pletsch, M.D., University of Kentucky, Lexington, Kentucky.

10:45 A.M.–11:00 A.M. The Effects of Radiation Therapy on Carcinoembryonic Antigen Titers in Cancer Patients. Sucha O. Asbell, M.D., The Hahnemann Medical College and Hospital of Philadelphia, Pennsylvania.

11:00 A.M.–11:15 A.M. Surgical Complications in a Combined High Dose Preoperative Irradiation—Composite Resection Program for Carcinoma of the Posterior Cavity. Robert H. Sagerman, M.D., Gerald A. King, M.D., Harvey M. Tucker, M.D., Daniel D. Rabuzzi, M.D. and George F. Reed, M.D., State University of New York, Syracuse, New York.

11:15 A.M.–11:30 A.M. A Quantative Study of Radiation Damage in Normal Tissues and Malignant Tumors. S. Rafla, M.D. and F. Abaci, M.D., The Methodist Hospital, Brooklyn, New York.

11:30 A.M.–11:45 A.M. Discussion

11:45 A.M.–12:00 NOON. Complications Following Head and Neck Surgery for Cancer. Donald G. Sessions, M.D., Joseph H. Ogura, M.D. and Alan M. Gall, M.D., Washington University, St. Louis, Missouri.

12:00 NOON–12:15 P.M. Radiation Induced Changes in the Tumor Microcirculation Which May Influence the Distribution of Chemotherapeutic Drugs. Richard Johnson, M.D., B. Pascall, M.D., H. Castro-Vita, M.D. and Mr. D. Boyle, Roswell Park Memorial Institute, Buffalo, New York.

12:15 P.M.–12:30 P.M. On the Treatment of Basophilic Adenomas of the Pituitary by Irradiation. An Analysis of the Relationships of Tumor Control and Complications to Time-Dose Factors. Silvio Aristizabal, M.D., William L. Caldwell, M.D., Jose Avila, M.D. and Eric Mayer, M.D., The University of Arizona, Tucson, Arizona.

12:30 P.M.–12:45 P.M. Management of Buccal Cavity Carcinoma Persistent After Full Tolerance Dose External Radiation and/or Surgery by Afterloading Interstitial IR 192 Implant. A. N. M. Syed, M.D., B. H. Feder, M.D. and F. W. George, III, M.D., University of Southern California, Los Angeles, California.

12:45 p.m.–1:00 p.m. Recent Developments at the Meson Radiotherapy Facility at TRIUMF. R. M. Henkelman, Ph.D. and L. D. Skarsgard, M.D., The British Columbia Cancer Institute, Vancouver, British Columbia.

1:00 p.m.–1:15 p.m. Discussion

Evening boat trip.

Tuesday, May 11, 1976

7:30 a.m.–8:30 a.m. First Executive Session. Breakfast Meeting for all members.

8:30 a.m.–1:00 p.m. Second Scientific Session. *Presiding;* Richard Jesse, M.D., Houston, Texas.

8:30 a.m.–10:00 a.m. *Symposium:* Soft Tissues in Children. *Moderator:* Luther Brady, M.D., Philadelphia, Pennsylvania.

10:00 a.m.–10:15 a.m. Solid Tumors of Childhood at Long Island Jewish Hillside Medical Center. I. Aral, M.D., C. Chong, M.D., P. Lanzkowsky, M.D. and S. Shende, M.D., Long Island Jewish Hillside Medical Center, Sea Cliff, New York.

10:15 a.m.–10:30 a.m. Intergroup Rhabdomyosarcoma Study: The Role of Radiation Therapy in Patients with Gross Residual Disease. Melvin Tefft, M.D. and Carlos H. Fernandez, M.D., Memorial Sloan-Kettering Cancer Center, New York, New York.

10:30 a.m.–10:45 a.m. Intermission

10:45 a.m.–11:00 a.m. The Evolution of a Treatment Program for Genitourinary Rhabdomyosarcoma in Children. R. Weichselbaum, M.D., J. R. Cassady, M.D., R. M. Filler, M.D. and N. Jaffe, M.D., Harvard Medical School, Boston, Massachusetts. (Sponsored by Martin B. Levene, M.D.)

11:00 a.m.–11:15 a.m. Discussion

11:15 a.m.–11:30 a.m. Stages I–III Hodgkin's Disease in Children: Results of Staging and Treatment. Robert Goodman, M.D., Norman Jaffee, Ph.D., B. Chem, M.D., Robert Filler, M.D. and Robert Cassady, M.D., Harvard Medical School, Boston, Massachusetts.

11:30 a.m.–11:45 a.m. How Do You Treat Hodgkin's Disease, Stage I and II? Arvin S. Glicksman, M.D. and Banice M. Webber, M.D., Rhode Island Hospital, Providence, Rhode Island.

11:45 a.m.–12:00 noon. Chronic Myelogenous Leukemia: Management of Splenectomy in High Risk Population. Charles M. McBride, M.D. and Jeane P. Hester, M.D., The University of Texas System Cancer Center, M. D. Anderson Hospital and Tumor Institute, Houston, Texas. (Sponsored by Richard H. Jesse, M.D.)

12:00 noon–12:15 p.m. The Management of Extramedullary Disease in Acute Leukemia with Radiotherapy. Harvey A. Gilbert, M.D., A. Robert Kagan, M.D., Robert Shapiro, M.D., Melville Jacobs, M.D. and Roland Skeel, M.D., Southern California Permanente Medical Group, Los Angeles, California.

12:15 p.m.–12:30 p.m. Squamous Cell Carcinoma of the Tonsil in Young Patients. William D. Johnston, M.D. and Robert M. Byers, M.D., The University of Texas System Cancer Center, M. D. Anderson Hospital and Tumor Institute, Houston, Texas.

12:30 p.m.–12:45 p.m. Radical Irradiation for Carcinoma of the Tonsil. Francis S. Cardinale, M.D. and James J. Fischer, M.D., Yale University School of Medicine, New Haven, Connecticut.

12:45 p.m.–1:00 p.m. Discussion

Afternoon trip to Victoria.

Wednesday, May 12, 1976

7:30 a.m.–8:30 a.m. Second Executive Session. Breakfast Meeting for all members.

8:30 a.m.–1:30 p.m. Third Scientific Session. *Presiding;* Antolin Raventos, M.D., Davis, California.

8:30 a.m.–10:00 a.m. *Symposium:* Carcinoma of the Prostate. *Moderator:* Douglas Johnson, M.D., Houston, Texas.

10:00 a.m.–10:15 a.m. Definite Radiation Therapy in Carcinoma of the Prostate Clinically Localized to the Pelvis. Carlos A. Perez, M.D., Robert K. Royce, M.D. and Walter C. Bauer, M.D., Washington University, St. Louis, Missouri.

10:15 a.m.–10:30 a.m. The Post-Irradiation Follow-up of Carcinoma of the Prostate. John Logan, M.D., J. Fenimore Cooper, M.D., Jack Gordon, M.D. and A. Robert Kagan, M.D., Southern California Permanente Medical Group, Los Angeles, California.

10:30 a.m.–10:45 a.m. Intermission

10:45 a.m.–11:00 a.m. Radiation Dose Effects in Pelvic Genitourinary Malignancies. G. B. Goodman, M.D., J. Balfour, M.D. and B. G. Douglas, M.D., Cancer Control Agency of British Columbia, Vancouver, British Columbia. (Sponsored by J. M. W. Gibson, M.D.)

11:00 a.m.–11:15 a.m. Discussion

11:15 a.m.–11:30 a.m. The Radio-Response of Cancer of the Prostate—An Analysis of 364 Cases. J. Bohorquez, M.D., R. Cabrera, M.D., K. Sahoo, M.D. and A. Lui, M.D., State University of New York, Brooklyn, New York.

11:30 a.m.–11:45 a.m. Staging and Localization of Tumors by Gallium^{67}—Subtraction Scanning. Yosh Maruyama, M.D., Frank H. Deland, M.D., J. R. van Nagell, Jr., M.D. and Robert M. Beihn, M.S., University of Kentucky, Lexington, Kentucky.

11:45 a.m.–12:00 noon. Intravenous Hyperalimentation as an Adjunct to Radiation Therapy. Edward M. Copeland, M.D., Eduardo M. Souchon, M.D., Bruce V. MacFadyen, M.D., Mary Ann Rapp, R.N. and Stanley J. Dudrick, M.D., The University of Texas System Cancer Center, M. D. Anderson Hospital and Tumor Institute, Houston, Texas.

12:00 NOON–12:15 P.M. Discussion

12:15 P.M.–12:30 P.M. Residents Award.

12:30 P.M.–12:45 P.M. The Preliminary Results of Randomized Trial of Patients with Late Stage Cancer of the Uterine Cervix Using Hyperbaric Tank or Atmospheric Oxygen Pressure. Gilbert H. Fletcher, M.D., Robert D. Lindberg, M.D., Jesus Caderao, M.D. and J. Taylor Wharton, M.D., The University of Texas System Cancer Center, M. D. Anderson Hospital and Tumor Institute, Houston, Texas.

12:45 P.M.–1:00 P.M. Carcinoma of the Cervix, Stage I, The Ellis Fischel Experience: Radium Therapy and Survival and External Radiotherapy Treatment Policies and Survival. James M. Thomson, M.D., John Spratt, Jr., M.D. and Richard J. LeDuc, M.D., Confederate Memorial Medical Center, Shreveport, Louisiana.

1:00 P.M.–1:15 P.M. Use of the Pig as an Experimental Model for Long Term Studies of Radiation Effects on Normal Tissues. J. C. Probert, M.D., C. M. Siu, M.D., H. S. Saben, Ph.D. and C. J. Gregory, Ph.D., Cancer Control Agency of British Columbia, Vancouver, British Columbia.

1:15 P.M.–1:30 P.M. Discussion

7:00 P.M. Reception

8:00 P.M. Annual Banquet.

Thursday, May 13, 1976

8:00 A.M.–1:15 P.M. FOURTH SCIENTIFIC SESSION. *Presiding;* Victor Marcial, M.D., San Juan, Puerto Rico.

8:00 A.M.–9:30 A.M. *Symposium:* Cancer of the Ovary. *Moderator:* Julian P. Smith, M.D., Houston, Texas. *Participants:* David Decker, M.D., Mayo Medical School, Rochester, Minnesota; Robert Young, M.D., National Cancer Institute, National Institute of Health, Bethesda, Maryland; and Zvi Fuks, M.D., Stanford University Medical Center, Stanford, California.

9:30 A.M.–9:45 A.M. Surgery, Chemotherapy and Super Voltage Radiotherapy for Carcinoma of the Ovary. Won K. Tak, M.D., Mary E. Costanza, M.D., George W. Mitchell, M.D., Fernando G. Bloedorn, M.D., Douglas J. Marchant, M.D., Larry Nathanson, M.D. and John E. Munzenrider, M.D., Tufts University School of Medicine, Boston, Massachusetts.

9:45 A.M.–10:00 A.M. Postoperative Pelvic Irradiation of Stage II Ovarian Carcinoma. P. E. Wallner, D.O., L. W. Brady, M.D., R. C. Nuss, M.D., G. C. Lewis, Jr., M.D., J. Antoniades, M.D., S. Prasasvinichai, M.D., S. Abell, M.D., J. Glassburn, M.D. and J. Damsker, M.D., The Hahnemann Medical College and Hospital of Philadelphia, Philadelphia, Pennsylvania.

10:00 A.M.–10:15 A.M. The Use of Laparoscopy in the Evaluation and Treatment of Early Ovarian Cancer. J. L. Cope, M.D. and D. A. Boyes, M.D., Cancer Control Agency of British Columbia, Vancouver, British Columbia.

10:15 A.M.–10:30 A.M. Discussion

10:30 A.M.–10:45 A.M. Intermission

10:45 A.M.–11:45 A.M. THE JANEWAY LECTURE. Pediatric Cancer Treatment: A Model for Oncology. Audrey Evans, M.D., Children's Hospital, Philadelphia, Pennsylvania.

11:45 A.M.–12:00 NOON. Installation of Officers

12:00 NOON–12:15 P.M. Management and Results of Endometrial Carcinoma Treated At Instituto Portugues de Oncologia de Francisco Gentil, Lisboa, Portugal. Maria Aida Tavares, M.D., Maria Brites Patricio, M.D., Mario Vilhena, M.D. and J. Neves da Silva, M.D., Instituto Portugues de Oncologia de Francisco Gentil, Lisboa, Portugal.

12:15 P.M.–12:30 P.M. Forty Years' Evolution in the Management of Patients with Endometrial Carcinoma. Orliss Wildermuth, M.D., Tumor Institute of the Swedish Hospital Medical Center, Seattle, Washington.

12:30 P.M.–12:45 P.M. Combined Therapy for Endometrial Cancer: Preoperative Intracavitary Irradiation Promptly by Hysterectomy. Joel D. Ohlsen, M.D., G. H. Johnson, M.D., J. R. Stewart, M.D., James R. Eltringham, M.D. and M. A. Stenchever, M.D., The University of Utah, Salt Lake City, Utah.

12:45 P.M.–1:00 P.M. Discussion.

1:00 P.M. Adjournment of the Fifty-eighth Annual Meeting.

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NEWS ITEMS

53RD ANNUAL MEETING, AMERICAN COLLEGE OF RADIOLOGY

The American College of Radiology will conduct its 53rd Annual Meeting, March 28–April 1, 1976 at the Washington Hilton Hotel, Washington, D.C.

All sessions are open. Members of the College in particular are urged to attend the sessions of the Council Reference Committees on Monday, March 29, 1976 to offer information, advice and opinion on business that comes before each Reference Committee.

Gold Medals, as well as Honorary Fellowship and Fellowship, will be awarded at the Convocation ceremony on Tuesday, March 30th. The Gold Medalists for 1976 are Drs. Robert P. Barden, C. Allen Good and Harold O. Wyckoff.

A categorical course on diagnostic ultrasound, which is approved for 12 hours of Category 1 credit, will be held during the ACR Annual Meeting.

The course, which will be chaired by Drs. Atis K. Freimanis and George R. Leopold, will explain the principles of diagnostic ultrasound, present information as to the current state of the art, discuss recent developments concerning the modality, and indicate future trends and potential.

For further information, please contact: American College of Radiology, 20 North Wacker Drive, Chicago, Illinois 60606.

DIAGNOSTIC ONCOLOGIC RADIOLOGY—II

The Department of Radiology and the Department of Postgraduate Education at Boston University School of Medicine will sponsor a course entitled "Diagnostic Oncologic Radiology: Current Concepts in Radiologic and Para-radiologic Diagnosis of Cancer."

The course will be held in Boston, Massachusetts, March 11–13, 1976 under the direction of Ernest J. Ferris, M.D. and Jerome H. Shapiro, M.D.

The course is designed to keep the radiologist abreast of the current concepts in cancer diagnosis and the status of new developments in this field.

There are 20 Category 1 credits for the Physician's Recognition Award for this course.

For further information, please contact: Daniel S. Bernstein, M.D., Department of Postgraduate Education, Boston University Medical Center, School of Medicine, 720 Harrison Avenue/Suite 206, Boston, Massachusetts 02118.

DIAGNOSTIC NUCLEAR IMAGING

A distinguished guest faculty joins specialists of the University of California at San Francisco in presenting topics of wide interest in Nuclear Medicine. As in the past, the presentations will focus generally on nuclear imaging procedures. It will be held March 13–14, 1976.

The course is held in conjunction with the Nineteenth Annual Diagnostic Radiology postgraduate course, March 15–19, 1976 at the Fairmont Hotel, California and Powell Streets, San Francisco, California. Consequently, special emphasis will be placed on several points of interaction between Nuclear Medicine and Diagnostic Radiology.

This program is presented by the Department of Radiology, Division of Nuclear Medicine and Extended Programs in Medical Education, University of California School of Medicine, San Francisco, California. It is acceptable for eight and one-half hours of Category 1 credit towards the certificate in Continuing Education for the American Medical Association and the California Medical Association. Program chairmen will be Paul B. Hoffer, M.D. and David C. Price, M.D.

To obtain further information regarding registration and program information, please contact: Extended Programs in Medical Education, Room 135G-C, University of California, San Francisco, California 94143.

RADIOLOGY OF THE ADULT CHEST

The American College of Radiology announces the first and second symposia in the series," Radiology of the Adult Chest." The Symposia will be held May 14–16, 1976 in Atlanta, Georgia and September 10–12, 1976 in Chicago, Illinois.

This series of seminars will use the same multiple viewbox technique devised by the American College of Radiology for weekend courses which has proved very successful in the past.

This ACR Symposium on The Adult Chest will attempt to provide an overview of thoracic radiology. The primary aim of the symposium will be to review the radiological approach of the diagnosis and management of frequently encountered diseases of the lung and mediastinum. Newer concepts will, of course, be emphasized as well.

The faculty is headed by E. Robert Heitzman, Jr., M.D. Joining Dr. Heitzman on the faculty will be Drs. Benjamin Felson, Robert G. Fraser, Alexander Gottschalk, Richard H. Greenspan and Stuart S. Sagel.

This course has received AMA credit in Category 1 for the Physician's Recognition Award for 15 hours of credit. This credit may also be toward the ACR Requirement and for state and local organizations' requirements.

Because of the large amount of space required for the multiple viewbox technique of teaching, and the logistical problems of transporting and setting up the equipment and materials needed, attendance is limited to 200 registrants. Registrations will be accepted on a first come—first served basis.

All registrations and inquiries regarding these seminars should be sent to: The American College of Radiology, 6900 Wisconsin Avenue, Chevy Chase, Maryland 20015.

RADIOLOGY OF THE PEDIATRIC CHEST

The American College of Radiology announces a continuing series of Symposia—Radiology of the Pediatric Chest, April 9–11, 1976 at Las Vegas, Nevada. An established format will be followed. The meeting will be on the weekend, allowing one to attend his practice, as well as his continuing education.

The course will cover Obstructing Lesions of the Airway; Inflammatory Disease; Systemic Diseases as Manifested in the Chest; Thoracic and Mediastinal Masses; and Conditions Peculiar to the Newborn Infant. The faculty is headed by John A. Kirkpatrick, Jr., M.D., and Donald H. Altman, M.D., Co-Chairmen. They will be joined by David Baker, M.D., John Gwinn, M.D., and Edward Singleton, M.D.

This course has received AMA credit in Category 1 for the ACR Requirement and the Physician's Recognition Award for 15 hours of credit. This credit may also be used for state and local organizations' requirements.

For further information, please contact: The American College of Radiology, 6900 Wisconsin Avenue, Chevy Chase, Maryland 20015.

RADIOLOGY OF THE GENITO-URINARY SYSTEM

The American College of Radiology announces the third symposium in the series, "Radiology of the Genitourinary System." The Symposium will be held in San Francisco, California, October 15–17, 1976.

The symposium will encompass renal parenchymal disease, mass lesions of kidney and the lower urinary tract, utilizing standard radiographic techniques and specialized procedures when appropriate. It will also include discussions on techniques of urography and angiography and reactions to contrast material. The faculty is headed by Thomas F. Meaney, M.D. Joining Dr. Meaney on the faculty will be Drs. David H. Baker, Joshua A. Becker, Anthony F. Lalli, Harry Z. Mellins and David M. Witten.

This course has received AMA credit in Category 1 for the ACR Requirement and the Physician's Recognition Award for 15 hours of credit. This credit may also be used for state and local organizations' requirements.

All registrations and inquiries regarding these seminars should be sent to: The American College of Radiology, 6900 Wisconsin Avenue, Chevy Chase, Maryland 20015.

NEURORADIOLOGY

This postgraduate course in neuroradiology is organized by the Department of Radiology of the Albert Einstein College of Medicine and its affiliated hospitals. It will be held May 10–14, 1976 at the Hotel Roosevelt, Madison Avenue and 45th Street, New York, New York. The course is intended for radiologists, neurologists, and neurosurgeons, and will be a comprehensive review of the present day concepts of diagnostic neuroradiology. Attention will also be directed towards the practical aspects of specialized diagnostic procedures. Film interpretation panels will emphasize the approach towards diagnostic problems. Computerized Axial Tomography will be discussed along with the individual topics.

The Continuing Medical Education Programs of the Albert Einstein College of Medicine have been accredited by the Council on Medical Education of the American Medical Association for Category 1 award and is acceptable for credit towards the American Medical Association Physician's Recognition Award. Thirty hours of credit are available for this course.

The program chairmen will be Milton Elkin, M.D. and Harold G. Jacobson, M.D.

For further information regarding application and registration, please contact: Mrs. Claire Delman, Program Administrator, Neuroradiology Postgraduate Course, Albert Einstein College of Medicine, Bronx, New York 10461.

A PRACTICAL COURSE IN ULTRASOUND

This one and one-half day course offers a survey of currently used techniques in ultrasound. It is designed to satisfy the needs of physicians and technicians who are interested in practicing ultrasound and for those with limited experience in ultrasound. The course is to be held March 20–21, 1976 at the Fairmont Hotel, California and Powell Streets, San Francisco, California.

The first day will consist of lectures covering practical approaches to ultrasound.

The second day will be a half-day of workshops with course participants attending four separate workshops. Equipment will be demonstrated on live models.

This program is presented by the Department of Radiology, University of California School of Medicine, and Extended Programs in Medical Education, San Francisco, California. It is acceptable for Category 1 credit towards the certificate in Continuing Education for the California Medical Association and the American Medical Association.

For further information regarding the course, please contact: Roy A. Filly, M.D., Program Chairman, Extended Programs in Medical Education, Room C-135G, University of California, San Francisco, California 94143.

VII INTERNATIONAL CONGRESS OF RADIOLOGY IN OTO-RHINO-LARYNGOLOGY

The VII International Congress of Radiology in Oto-Rhino-Laryngology is planned to take place in Copenhagen, Denmark, May 31–June 2, 1976 under the presidency of Dr. Sam Brunner.

The following are the main themes: Computer-assisted Axial Tomography in O.R.L.;

Thermography and Xeroradiography in O.R.L.; Liquor Fistulas in O.R.L.; Lesions of the Facial Nerve Canal; Meniere's Disease; Malignant and Semimalignant Tumors of the Nasal and Paranasal Cavities; Tumors of the Rhinopharynx.

For further information, please contact: Dr. Paul E. Andersen, Department of Radiology, University Hospital, 5000 Odense, Denmark.

POSTGRADUATE COURSE IN TOMOGRAPHY OF THE TEMPORAL BONE

In connection with the VII International Congress of Radiology in Oto-Rhino-Laryngology, a Postgraduate Course in Tomography of the Temporal Bone will be held in Copenhagen, June 3–4, 1976.

The course is sponsored by the I.C.R., the A.E.R. and the Scandinavian Association of Radiologists and will be directed by Dr. Sam Brunner, President of the Congress.

Experts in the various fields will lecture on the techniques, diagnostic findings interpretations, advantages and limitations of the different procedures.

For further information and registration, please contact: Dr. Paul E. Andersen, Department of Radiology, University Hospital, 5000 Odense, Denmark.

EUROPEAN SEMINAR ON COMPUTERIZED AXIAL TOMOGRAPHY IN CLINICAL PRACTICE

The first European seminar on the clinical application of C. A. T. (EMI Scanning) will be held in London, October 11–15, 1976.

The faculty will be drawn mainly from the principal European countries engaged in the use and development of this technique. The emphasis will be on clinicoradiological collaboration, and although most of the speakers will deal with craniocerebral scanning, up to one and one-half days will be devoted to whole-body examination methods.

Full details of the programme and registration arrangements can be obtained from: Dr. I. F. Moseley, Lysholm Radiological Department, National Hospital for Nervous Diseases, Queen Square, London W. C. 1, England.

GENITOURINARY RADIOLOGY

The New York Medical College is sponsoring a course on Genitourinary Radiology at the Plaza Hotel, New York, New York, on April 5–7, 1976.

For further information, please contact: Richard M. Friedenberg, M.D., Department of Radiology, New York Medical College, Fifth Avenue at 106th Street, New York, New York 10029.

GENERAL DIAGNOSTIC RADIOLOGY REFRESHER COURSE

A three day course in General Diagnostic Radiology will be held at the Bayshore Inn, Vancouver, British Columbia, Canada on May 19–21, 1976.

The course will present current concepts and recent advances in chest, gastrointestinal, and bone and joint radiology, including a session on practical techniques in diagnostic radiology.

The course is approved for 18 hours of credit in Category 1 for the Physicians recognition award of the American Medical Association.

For further information, please contact: D. Gordon Garrow, M.B., Department of Radiology, University of British Columbia, 10th Avenue and Heather Street, Vancouver, British Columbia, Canada.

INTERNATIONAL SYMPOSIUM ON COMPUTER ASSISTED TOMOGRAPHY AT THE NATIONAL INSTITUTES OF HEALTH

An International symposium on "Computer Assisted Tomography in Nontumoral Diseases of the Brain, Spinal Cord and Eye," sponsored by the National Institute of Neurological and Communicative Disorders and Stroke is announced. The meeting will be held at the Clinical Center on the campus of the National Institutes of

Health, Bethesda, Maryland, USA, October 12–15, 1976, under the chairmanship of Giovanni Di Chiro, M.D.

The topics will include the physics, technologies (various devices and modalities), and the clinical (morphological and functional) aspects of transmission and emission computer assisted tomography of the brain, spinal cord and eye, with emphasis on nontumoral diseases.

Investigators are invited to submit detailed and documented abstracts (data, illustrations). The deadline is August 1, 1976. Inclusion in the program will be established solely on scientific criteria.

Scientific and technical exhibits are planned.

For further information, please contact: Giovanni Di Chiro, M.D., National Institutes of Health, Section on Neuroradiology, Clinical Center, Room 2D13, Bethesda, Maryland 20014.

BOOKS RECEIVED

CARDIAC ULTRASOUND. Edited by Raymond Gramiak, M.D., Professor of Diagnostic Radiology, University of Rochester, School of Medicine; Radiologist, Strong Memorial Hospital, Rochester, N. Y.; and Robert C. Waag, Ph.D., Department of Electrical Engineering, College of Engineering and Applied Sciences; Department of Radiology (Diagnostic), University of Rochester, Rochester, N. Y.; with 18 contributors. Cloth. Pp. 308, with 465 illustrations. Price, $34.50. C. V. Mosby Company, 3301 Washington Boulevard, St. Louis, Mo. 63103, 1975.

CANCER CHEMOTHERAPY. Second edition. By Martin J. Cline, M.D., Bowyer Professor of Medical Oncology; Chief, Division of Hematology-Oncology, Department of Medicine, University of California, Los Angeles, The Center for the Health Sciences, Los Angeles, Calif.; and Charles M. Haskell, M.D., Assistant Professor of Medicine and Surgery, Department of Medicine, University of California, Los Angeles, The Center for the Health Sciences, Los Angeles, Calif. Cloth. Pp. 324, with some illustrations. Price, $16.00. W. B. Saunders Company, West Washington Square, Philadelphia, Pa. 19105, 1975.

SKELETAL PROJECTIONS FOR DIAGNOSTIC RADIOLOGY. By Anders Movin, M.D., Department of Diagnostic Radiology, Eskilstuna Lasarett, Eskilstuna, Sweden; and Ulf Karlsson, M.D., Ph.D., Professor of Anatomy, Department of Anatomy, College of Medicine, The University of Iowa; Professor of Pedodontics, Department of Pedodontics, College of Dentistry, The University of Iowa, Iowa City, Iowa. Paper. Pp. 264, with 214 illustrations. Price, $19.00. J. B. Lippincott Company, East Washington Square, Philadelphia, Pa. 19105, 1975.

PRIMER OF MEDICAL RADIOBIOLOGY. By Elizabeth Latorre Travis, Associate, Department of Radiology, Division of Radiologic Sciences, Medical University of South Carolina, Charleston, S. C. Cloth. Pp. 241, with some illustrations. Year Book Medical Publishers, Inc., 35 East Wacker Drive, Chicago, Ill. 60601, 1975.

TECHNOLOGY AND INTERPRETATION OF NUCLEAR MEDICINE PROCEDURES. By D. Bruce Sodee, M.D., F.A.C.P., F.A.C.G., A.B.N.M., Director, Nuclear Medicine Institute; Director, Nuclear Medicine Department, Hillcrest Hospital, Cleveland Memorial Foundation, Cleveland, Ohio; and Paul J. Early, B.S., President, Nuclear Medicine Associates, Inc., Cleveland, Ohio; with the technical assistance of Ashwin Patel, B.S., R.T. (A.R.R.T.). Second edition. Cloth. Pp. 520, with many illustrations. Price, $26.50. C. V. Mosby Company, 3301 Washington Boulevard, St. Louis, Mo. 63103, 1975.

SOCIETY PROCEEDINGS

MEETINGS OF RADIOLOGICAL SOCIETIES*

United States of America

American Roentgen Ray Society
Secretary, Dr. James Franklin Martin, 300 S. Hawthorne Rd., Winston-Salem, N. C. 27103. Annual Meeting: Washington Hilton, Washington, D. C., Sept. 20–24, 1976.

American Radium Society
Secretary, Richard H. Jesse, Dept. of Surgery, M. D. Anderson Hosp. and Tumor Institute, Houston, Tex. 77025. Annual Meeting: Bayshore Inn, Vancouver, B. C., Canada, May 9–14, 1976.

Radiological Society of North America
Secretary, Dr. Theodore A. Tristan, Harrisburg, Pennsylvania.

American College of Radiology
Executive Director, William C. Stronach, 20 N. Wacker Drive, Chicago, Ill. 60606. Annual meeting.

Section on Radiology, American Medical Association
Secretary, Dr. Antolin Raventos, Davis, Calif. Annual Meeting.

American Board of Radiology
Secretary, Dr. C. Allen Good. Correspondence should be directed to Kahler East, Rochester, Minn. 55901.
Oral examinations will be held: Marriott Motor Hotel, Chicago, Ill., June 14–19, 1976; Sheraton Biltmore, Atlanta, Ga., Dec. 6–11, 1976.
Written examinations will be held in 14 selected sites on June 26, 1976.
Applications must be received in the Board Office before Sept. 30 of the year preceding the one in which the candidate wishes to be examined.

American Board of Nuclear Medicine, Inc. A Conjoint Board of the American Boards of Internal Medicine, Pathology and Radiology and sponsored by the Society of Nuclear Medicine.
Application forms and further information are available from the American Board of Nuclear Medicine, 305 E. 45th St., New York, N. Y. 10017.

American Association of Physicists in Medicine
Secretary, Dr. Robert G. Waggener, Dept. Radiol., Univ. Tex. Health Sciences Center, San Antonio, Tex. 78284 Annual Meeting:

American Society of Therapeutic Radiologists
Secretary, Dr. Robert W. Edland, 1836 South Ave., La Crosse, Wis., 54601. Annual Meeting:

American Nuclear Society
Program Chairman, Werner K. Kern, IRD, Space Nuclear Systems, F 309, U. S. Atomic Energy Commission, Washington, D.C. 20545.

American Institute of Ultrasound in Medicine
Secretary, John M. Reid, Ph.D., 556 18th Ave., Seattle, Wash. 98122. Annual Meeting.

American Society of Neuroradiology
Secretary, Arthur E. Rosenbaum, University of Pittsburgh, Pittsburgh, Pa. 15261. Annual Meeting: Peachtree Plaza Hotel, Atlanta, Ga., May 18–22, 1976.

Fourteenth International Congress of Radiology
Rio de Janeiro, Brazil, Oct. 23–29, 1977.
President Elect: Prof. Dr. Nicola C. Caminha; *General Secretary:* Dr. Durval Couto. Av. Churchill, 97-50 and LC-39 20,000 Rio de Janeiro, Brazil.

International Society of Radiology
Hon. Secretary-Treasurer, Prof. W. A. Fuchs, M.D., Department of Diagnostic Radiology, University Hospital, Inselspital, CH-3010 Bern, Switzerland.

Twelfth Inter-American Congress of Radiology
President, Dr. Publio Vargas Pazzos, Casilla 5227, Guayaquil, Ecuador. Meeting in Quito, Ecuador, 1979.

Inter-American College of Radiology
President, Manuel Viamonte, Jr., M.D., Mt. Sinai Medical Center, 4300 Alton Rd., Miami Beach, Fla. 33140.
Secretary, Gaston Morillo, M.D., Jackson Memorial Hosp., 1700 N.W. 10th Ave., Miami, Fla. 33152.
Counselor for the United States, J. A. del Regato, M.D., Univ. of So. Fla. College of Medicine, 13000 No. 30th St., Tampa, Fla. 33612.

Third Congress of the European Association of Radiology
Secretary-General, P.O. Box 14, 79 Lauriston Place, Edinburgh BHI IDB, Scotland.

Second Asian and Oceanian Congress of Radiology
Secretary, Dr. Buenaventura U. V. Angtuaco, Congress Secretariat Headquarters, 2161 Taft Ave., Manila, Philippines.

Alabama Chapter of ACR
Secretary-Treasurer, Dr. Lawrence E. Fetterman, 1720 Springhill Ave., Suite 201, Mobile, Ala. 36604. Meets time and place of Alabama State Medical Association.

Alaska Radiological Society, Chapter of ACR
Secretary-Treasurer, Dr. Maurice J. Coyle, 3200 Providence Ave., Anchorage, Alaska 99504.

American Osteopathic College of Radiology
Annual Scientific Meeting: Americana Hotel, Bar Harbor, Fla. Program Administrator: Lawrence J. Jordan, D.O., Suite 21, Ponce American Bldg., 4601 Ponce de Leon Blvd., Coral Gables, Fla. 33146.

American Thermographic Society
Secretary-Treasurer, John Wallace, Ph.D., Dept. Radiol., Thomas Jefferson Univ. Hosp., Philadelphia, Pa. 19107. Annual Meeting.

Arizona Radiological Society, Chapter of ACR
Secretary, Dr. Irwin M. Freundlich, 1501 N. Campbell Ave., Dept. Radiol., Tucson, 85724. Two regular meetings a year. Annual meeting at time and place of State Medical Association and interim meeting six months later.

Ark-La-Tex Radiological Society
Secretary, Dr. Erich K. Lang, 1541 Kings Highway, Shreveport, La. 71130. Meets monthly on fourth Wednesday, 8:00 P.M., Sept. to May.

Arkansas Chapter of ACR
Secretary-Treasurer, Dr. Richard Seibold, Jr., Wadley Hosp., Texarkana, Ark.—Tex. 75501. Meets twice annually, the Spring Meeting being in conjunction with and at the place of the State Medical Association.

Association of University Radiologists
Secretary-Treasurer, Dr. Arch W. Templeton, Univ. of Kansas Med. Center, 39th and Rainbow Blvd., Kansas City, Kansas 66103. Annual Meeting.

Atlanta Radiological Society
Secretary-Treasurer, Dr. James H. Larose, Dept. Nuclear Med., South Fulton Hosp., East Point, Ga. 30344. Meets on four Thursday evenings during the academic year at a time announced in early September of each year, at various Atlanta restaurants.

*** Secretaries of societies are requested to send timely information promptly to the Editor.**

Bavarian-American Radiologic Society
Secretary, LTC. Marco J. DiBiase, M.D., Radiology Service, Heidelberg, 130 Station Hosp., APO N. Y. 09102. Meets quarterly.

Blockley Radiological Society
Secretary-Treasurer, Dr William H. Green, 616 East 24th St., Chester, Pa. 19013.

Bluegrass Radiological Society
Secretary-Treasurer, Dr. Eugene Slusher, Lexington Clinic, 1221 S. Broadway, Lexington, Ky. 40504. The Society meets once each month during the school year.

Bronx Radiological Society, New York State, Chapter ACR
Secretary-Treasurer, Dr. Leon J. Corbin, 1369 Rosendale Ave., Bronx, N. Y. 10472. Meets 4 times a year.

Brooklyn Radiological Society
Secretary-Treasurer, Dr. Ralph Brancaccio, 7901 4th Ave., Brooklyn, N. Y. 11209. Meets first Thursday of each month, October through June.

Buffalo Radiological Society
Secretary, Dr. George J. Alker, Jr., E. J. Meyer Mem. Hosp., Buffalo, N. Y. 14215. Meets second Monday evening each month, October to May inclusive, at University Club.

California Radiation Therapy Association
Secretary-Treasurer, Dr. Duane J. Gillum, Stanford Medical Center, Stanford, Calif. 94304. Meets semiannually in San Francisco and Los Angeles.

California Radiological Society, California Chapter of ACR
Secretary-Treasurer, Dr. John L. Gwinn, 4650 Sunset Blvd., Los Angeles, Calif. 90027.

Catawba Valley Radiological Society
Secretary, Dr. Walter Joe Jacumin, P.O. Box 265, Rutherford College, N. C. 28671. Meets the last Thursday of every month, Holiday Inn, Morganton, N. C. at 7:30 p.m.

Central New York Radiological Society
Secretary-Treasurer, Dr. Alfred Brettner, Auburn Mem. Hosp., Auburn, N. Y. 13021. Meets first Monday each month October through May.

Central Ohio Radiological Society
Secretary-Treasurer, Dr. Daniel E. Lewis, 309 East State St., Columbus, Ohio 43215. Meets second Thursday in October, November, January, March, and May at Fort Hayes Hotel, Columbus, Ohio.

Central Texas Radiology Society
Secretary-Treasurer Dr. E. Jerome Schoolar, Scott and White Clinic, Temple, Tex. 76501. Meets the fourth Monday of each month at Ponderosa Hotel, Temple, Tex. at 7:00 p.m.

Chicago Radiological Society, Division of the Illinois Radiological Society, Chapter of ACR
Secretary-Treasurer, Dr. Harold J. Lasky, 55 E. Washington St., Suite 1735, Chicago, Ill. 60602. Meets third Thursday of each month, October to April, except December, at the Bismark Hotel, Chicago, Ill.

Cleveland Radiological Society
Secretary-Treasurer, Dr. Charles M. Greenwald, 7007 Powers Blvd., X-Ray Dept., Parma, Ohio 44129. Meetings at 7:00 p.m. on fourth Monday of October, November, January, February, March and fifth Monday of April.

Colorado Radiological Society, Chapter of ACR
Secretary, Dr. John Pettigrew, Denver, Colo. Meets third Friday of each month at Denver Athletic Club from September through May.

Connecticut Valley Radiologic Society
Secretary, Dr. Gerald N. LaPierre, 759 Chestnut St., Springfield, Mass. 01107. Meets in April and October.

Dallas-Fort Worth Radiological Society
Secretary-Treasurer, Dr. Robert R. Burns, 1400 Stemmons Ave., Dallas, Tex. 75208. Meets the 3rd Monday of every month at 6:30 p.m., at the Airport Hotel, Arlington, Tex.

Delaware Chapter of ACR
Secretary, Dr. Ekkehard S. Schubert, Wilmington Med. Center, P. O. Box 1951, Wilmington, Del. 19899.

East Bay Radiological Society
Secretary-Treasurer, Dr. Richard H. Culhane, 4 Vista del Mar, Orinda, Calif. 74563. Meets first Thursday each month, Oct. through May, at University Club, Oakland Calif.

East Tennessee Radiological Society
Secretary-Treasurer, Dr. George H. Wood, 205 Medical Arts Bldg., Knoxville, Tenn. 37902. Meets in January and September.

Florida Radiological Society, Chapter of ACR
Secretary. Dr. Paul J. Popovich, 1350 S. Hickory St., Melbourne, Fla. 32901. Meets twice annually, in the spring with the Annual State Society Meeting and in the fall.

Florida West Coast Radiological Society
Secretary-Treasurer, Dr. Herbert Johnson, Davis Blvd., Tampa, Fla. 33606. Meets on 4th Thursday of the months January, March, May, October, and November.

Georgia Radiological Society, Chapter of ACR
Secretary, Dr. E. P. Rasmussen, Piedmont Prof. Bldg., 35 Collier Rd., N.W., Atlanta, Ga. 30309.

Greater Cincinnati Radiological Society
Secretary-Treasurer, Dr. Owen L. Brown, 2421 Auburn Ave., Cincinnati, Ohio 45219.

Greater Kansas City Radiological Society
President-Secretary, Dr. Jay I. Rozen, Suite 216, 6400 Prospect, Kansas City, Mo. 64132. Meets 5 times a year.

Greater Louisville Radiological Society
Secretary-Treasurer, Dr. L. D. LeNeave, 315 E. Broadway, Louisville, Ky. 40202. Meets monthly.

Greater Miami Radiological Society
Secretary, Dr. David C. Hillman, P. O. Box 610544, North Miami, Fla. 33161. Meets monthly, third Wednesday at 8:00 p.m. at various member hospitals, Miami, Fla.

Greater St. Louis Society of Radiologists
Secretary-Treasurer, Dr. Donald Callahan, Northland Med. Bldg., Jennings, Mo. 63136.

Hawaii Radiological Society, Chapter of ACR
Secretary-Treasurer, Dr. Michael J. McCabe, Straub Clinic and Hosp., Honolulu, Hawaii 96813. Meets third Monday of each month at 7:00 p.m.

Health Physics Society
Secretary, Russell F. Cowing, P.O. Box 156, E. Weymouth, Mass. 02189. Annual Meeting.

Houston Radiological Society
Secretary, Dr. Neill B. Longley, 6436 Fannin, Suite 601, Houston, Tex. 77025. Meets fourth Monday of each month, except June, July, August and December, at 6:00 p.m., at 103 Jesse H. Jones Library Building, Texas Medical Center, Houston, Tex. 77025.

Idaho State Radiological Society, Chapter of ACR
Secretary-Treasurer, Dr. John H. Truksa, 1605 Park Ave., Nampa, Id. 83651. Meets in the spring and fall.

Illinois Radiological Society, Inc., Chapter of ACR
Secretary, Dr. Robert D. Dooley, Hinsdale Med. Center, Hinsdale, Ill. 60521. Meets in the spring and fall.

Indiana Roentgen Society, Inc., Chapter of ACR
Secretary, Dr. John A. Knote, Home Hosp., Lafayette, Ind. 47902.

Iowa Radiological Society, Chapter of ACR
Secretary-Treasurer, Dr. Dale L. Roberson, 1948 First Ave., NE, Cedar Rapids, Iowa 52402. Luncheon and business meeting during annual session of Iowa State Medical Society. The scientific session is held in the autumn.

Kansas Radiological Society, Chapter of ACR
Secretary-Treasurer, Dr. Ralph H. Baehr, 310 Medical Arts Bldg., Topeka, Kan. 66604. Meets in spring with State Medical Society and in winter on call.

Kentucky Chapter of ACR
Secretary-Treasurer, Dr. Bernard Sams, St. Joseph In-

firmary, 735 Eastern Parkway, Louisvlle, Ky. 40217. Meets in April and September.

Kings County Radiological Society
Secretary, Dr. Sidney Hendler, 1880 Ocean Ave., Brooklyn 30, N. Y. Meets Kings County Med. Soc. Bldg. monthly on fourth Thursday, October to May, 8:45 P.M.

Knoxville Radiological Society
Secretary, Dr. Clifford L. Walton, Blount Professional Bldg., Knoxville 20, Tenn. Meetings are held the third Monday of every other month at the University of Tennessee Memorial Research Center and Hospital.

Long Island Radiological Society
Secretary, Dr. Harry L. Stein, North Shore Univ. Hosp., 300 Community Dr., Manhasset, N. Y. 11030.

Los Angeles Radiological Society
Secretary, Dr. Arthur F. Schanche, 333 North Prairie Ave., Inglewood, Calif. 90301. Meets second Wednesday of month in September, November, January, April and June at Los Angeles County Medical Association Building, Los Angeles, Calif. Midwinter Radiological Conference. Century Plaza Hotel, Los Angeles, Calif.

Louisiana Radiological Society, Chapter of ACR
Secretary-Treasurer, Dr. Roger H. Tutton, 1514 Jefferson Hwy., New Orleans, La. 70121.

Louisiana-Texas Gulf Coast Radiological Society
Secretary-Treasurer, Dr. J. Gardiner Bourque, 3155 Stagg Dr., Suite 230, Doctors Bldg., Beaumont, Texas 77701.

Maine Radiological Society, Chapter of ACR
Secretary-Treasurer, Dr. Peter E. Giustra, Dept. Radiology, Penobscot Bay Medical Center, Rockland, Maine 04841. Meets in June, September, December and April.

Maryland Radiological Society, Chapter of ACR
Secretary, Dr. David S. O'Brien, Anne Arundel Hosp., Annapolis, Md. 21401.

Massachusetts Radiological Society, Chapter of ACR
Secretary, Dr. Joseph T. Ferrucci, Jr., Massachusetts Gen. Hosp., Boston, Mass. 02114.

Memphis Roentgen Society
Secretary-Treasurer, Dr. R. Randolph Ramey, Baptist Memorial Hosp., 899 Madison Ave., Memphis, Tenn. 38146. Meets first Monday Oct. through June at the University Club.

Miami Valley Radiological Society
Secretary, Dr. Bert Must, I.B.M. Bldg., Dayton, Ohio. Meets third Thursday of fall, winter and spring months at 7:30 P.M. at Miami Valley Hospital, Dayton, Ohio.

Michigan Radiological Society, Chapter of ACR
Secretary-Treasurer, Dr. Francis P. Shea, Harper Hospital, 3825 Brush St., Detroit, Mich. 48201. Meets monthly, first Thursday, October through May, at David Whitney House, 1010 Antietam, at 6:30 P.M.

Michigan Society of Therapeutic Radiologists
Secretary-Treasurer, Dr. William I. Knapp, St. Mary's Hosp., 830 S. Jefferson, Saginaw, Mich. 48601. Meets bimonthly during the academic year.

Mid-Hudson Radiological Society
Secretary-Treasurer, Dr. William D. Stiehm, 37 Flower Hill Rd., Poughkeepsie, N. Y. 12603. Meets 7:00 P.M., first Wednesday of each month, September to May.

Milwaukee Roentgen Ray Society
Secretary-Treasurer, Dr. Thomas C. Lipscomb, 1004 North Tenth St., Milwaukee, Wis. 53233. Meets monthly on fourth Monday, October through May, at University Club.

Minnesota Radiological Society, Chapter of ACR
Secretary-Treasurer, Dr. Marvin E. Goldberg, Box 292, Mayo Memorial Health Sciences Center, Minneapolis, Minn. 55455.

Mississippi State Radiological Society, Chapter of ACR
Secretary-Treasurer, Dr. Edward L. Gieger, 969 Lakeland Dr., Jackson, Miss. 39216. Meets third Thursday, excluding summer months, at the Primos Northgate Rest., Jackson at 6:30 P.M.

Missouri Radiological Society, Chapter of ACR
Secretary-Treasurer, Dr. Ronald G. Evens, Mallinckrodt Institute of Radiology, 510 S. Kingshighway, St. Louis, Mo. 63110.

Montana Radiological Society, Chapter of ACR
Secretary, Dr. C. H. Agnew, Room 102, Doctors Bldg., Billings, Mont. 59101.

Nebraska Chapter of ACR
Secretary-Treasurer, Dr. Robert Bodmer, Suite 622 Doctors Bdg., Omaha, Neb. 68131. Meets the third Wednesday of the month, Oct. through March, at the Clarkson Hosp., Omaha, Neb. and the fourth Friday of April at the Lincoln Country Club, Lincoln, Neb.

Nevada Radiological Society, Chapter of ACR
Secretary, Dr. Charles F. Veverka, Carson Tahoe Hosp., Carson City, Nev. 89701.

N.E. Society for Radiation Oncology
Secretary, Dr. C. C. Wang, Mass. Gen. Hosp., Boston, Mass. 02114.

New England Roentgen Ray Society
Secretary, Dr. Melvin E. Clouse, 185 Pilgrim Rd., Boston, Mass. 02115. Meets the third Friday of Oct. and Nov., and third Thurs. of each month. Jan. through May, excluding December, at The Longwood Towers, 20 Chapel Street, Brookline, Mass. at 3:00 P.M. Annual Meeting: May 20, 1976.

New Hampshire Roentgen Ray Society, Chapter of ACR
Secretary-Treasurer, Dr. Edward P. Kane, Claremont Gen. Hosp., Claremont, N. H. 03743. Meets four to six times yearly.

New Mexico Society of Radiologists, Chapter of ACR
Secretary, Dr. W. M. Jordan, 1100 Central Ave. S.E., Albuquerque, N. M. 87106. Four meetings annually, three held in Albuquerque, N. M., and one held at time and place of New Mexico State Medical Society annual meeting.

New Orleans Radiological Society, Inc.
Secretary-Treasurer, Dr. Jimmy L. Mains, P.O. Box 446, Gretna, La. 70053. Meets bimonthly at local restaurants selected by the President. Spring Conference.

New York Roentgen Society
Secretary-Treasurer, Dr. Thomas C. Beneventano, 111 East 210th St., Bronx, N. Y. 10467. Meets monthly on the 3rd Monday at the New York Academy of Medicine at 4:30 P.M. Annual Spring Conference, Waldorf-Astoria Hotel, New York, N. Y., April 22–24, 1976. A.M.A. Cat. I credit. Further information may be obtained from Dr. Albert A. Dunn, Roosevelt Hosp., New York, N. Y. 10019.

New York State Chapter of ACR
Secretary-Treasurer, Dr. Albert F. Keegan, 6 Secor Dr., Port Wash., N. Y. 11050.

North American Society of Cardiac Radiology
Secretary-Treasurer, Dr. Erik Carlson, Univ. Calif., San Francisco, Calif. 94143.

North Carolina Chapter of ACR
Secretary-Treasurer, Dr. Ernest B. Spangler, Wesley Long Hosp., Greensboro, N. C. 27402. Meets twice a year. The Spring Meeting is held at the time of the meeting of the North Carolina Medical Society. The Fall Meeting is held in November at the Mid Pines Club, Southern Pines, N. C.

North Dakota Radiological Society, Chapter of ACR
Secretary, Dr. Marshall Landa, P. O. Box 6001, Fargo, N. D. 58102. Meets at time of State Medical Association meeting. Other meetings arranged on call of the President.

North Florida Radiological Society
Secretary, Dr. David F. Bew, University Hospital of

Jacksonville, 655 W. Eighth Street, P.O. Box 2751, Jacksonville, Fla. 32203. Meets quarterly in March, June, September and December.

Northeastern Oklahoma Radiological Society
Secretary-Treasurer, Dr. Theodore J. Brickner, Jr., 5919 S. Gary Place, Tulsa, Okla. 74110.

Northeastern New York Radiological Society
Secretary, Dr. Donald R. Morton, Dept. of Radiology, St. Clare's Hosp., Schenectady, N. Y. 12304. Meets in Albany area on third Wednesday of October, November, March, April, and May.

Northern California Radiation Therapy Association
Secretary-Treasurer, Dr. John D. Earle, Stanford Medical Center, Stanford, Calif. 94304. Meets quarterly.

Northern California Radiological Society
Secretary, Dr. Patrick J. Grinsell, 1207 Fairchild Ct., Woodland, Calif. 95695. Meets on the fourth Monday, Sept. through May at the Mansion Inn, Sacramento, Calif.

Northwestern New York Radiological Society
Secretary, Dr. Barbara E. Chick, Glens Falls Hospital, Glens Falls, N. Y. 12801.

Northwestern Ohio Radiological Society
Secretary, Dr. Richard W. Siders, 421 Michigan, Toledo, Ohio 43624. Meets 3rd Wednesday from September to May.

Ohio State Radiological Society, Chapter of ACR
Secretary, Dr. James Farmer, Cleveland, Ohio.

Oklahoma State Radiological Society, Chapter of ACR
Secretary, Dr. George H. Ladd, 4616 Denison, Muskogee, Okla. 74401. Meets in January, May and October.

Orange County Radiological Society
Secretary, Dr. William E. Danko, 2601 E. Chapman, Orange, Calif. 92667. Meets on fourth Tuesday of the month, excluding June, July, August, and December, at Orange County Medical Association Bldg., Orange, Calif.

Oregon State Radiological Society, Chapter of ACR
Secretary-Treasurer, Dr. Ray F. Friedman, 3324 S. W. 44th St., Portland, Ore. 97221. Meets on second Wednesday of month, October through April, at the University Club, Portland, Ore.

Orleans Parish Radiological Society
Secretary, Dr. Joseph V. Schlosser, Charity Hospital, New Orleans, La. 70113. Meets second Tuesday of each month.

Pacific Northwest Radiological Society
Secretary-Treasurer, Dr. Kenneth D. Moores, 1118 9th Ave., Seattle, Wash. 98101. Annual Meeting: Benson Hotel, Portland, Ore., May 7–9, 1976.

Pennsylvania Radiological Society, Chapter of ACR
Secretary, Dr. Joseph A. Marasco, Jr., St. Francis General Hosp., Pittsburgh, Pa. 19141.

Philadelphia Roentgen Ray Society
Secretary, Dr. Marvin E. Haskin, 230 N. Broad St., Philadelphia, Pa. 19102. Meets first Thursday of each month at 5 p.m., from October to May in Thompson Hall, College of Physicians.

Pittsburgh Roentgen Society
Secretary, Dr. Klaus M. Bron, Presbyterian-Univ. Hosp., Pittsburgh 15213. Meets second Wednesday of month, September through May, at the Pittsburgh Athletic Association.

Radiation Research Society
Executive Secretary, Richard J. Burk, Jr., 4211 39th St., N.W., Washington, D. C. 20016. Annual Meeting.

Radiological Society of Connecticut, Inc., Chapter of ACR
Secretary, Dr. Gerald L. Baker, 85 Jefferson St., Hartford, Conn. 06106. Meets in Oct., Jan., March, and June.

Radiological Society of Greater Cincinnati
Secretary-Treasurer, Dr. Alvin Nathan, c/o Academy of Medicine, 320 Broadway, Cincinnati, Ohio 45202. Meets first Monday of each month at Cincinnati Academy of Medicine.

Radiological Society of New Jersey, Chapter of ACR
Secretary, Dr. Fred M. Palace, 11 Dale Dr., Morristown, N.J. 07960. Monthly meetings in East Orange and Trenton, N.J. Semi-Annual Meeting in Nov.

Radiological Society of Rhode Island, Chapter of ACR
Secretary-Treasurer, Dr. Daniel J. Alves, Rhode Island Hosp., Providence, R. I. 02902.

Radiological Society of Southern California
Secretary-Treasurer, Dr. A. Franklin Turner, LAC-USC Medical Center, Room 3418, 1200 North State St., Los Angeles, Calif. 90033. Meets three times a year, usually October, February and May.

Radiological Society of the State of New York
Secretary-Treasurer, Dr. John W. Colgan, 273 Hollywood Ave., Rochester, N. Y. 14618.

Redwood Empire Radiological Society
Secretary, Dr. Charles E. Carter, 121 Sotoyome St., Santa Rosa, Calif. 95405. Meets second Monday every other month.

Richmond County Radiological Society
Secretary, Dr. Frederick S. Vines, 11830 Rothbury Dr., Richmond, Va. 23235. Meets third Thursday of each month at the Aberdeen Barn.

Rochester Roentgen Ray Society, Rochester, N. Y.
Secretary-Treasurer, Dr. Robert J. Bruneau, Rochester General Hosp., Rochester, N. Y. 14621. Quarterly meetings on the call of the President, at the Rochester Academy of Medicine.

Rocky Mountain Radiological Society
Secretary-Treasurer, Dr. Lorenz R. Wurtzebach, 4200 E. Ninth Ave., Denver, Colo. 80220. Annual Meeting: Brown Palace Hotel, Denver, Colo., Aug. 19–21, 1976.

San Antonio-Civilian Military Radiological Society
Secretary, Dr. James R. Stewart, Oak Hills Medical Ctr., San Antonio, Tex. 78209. Meets third Wednesday of each month at Fort Sam Houston Officers Club at 6:30 p.m.

San Diego Radiological Society
President, Dr. Donald J. Fleischli, 7849 Fay Ave., La Jolla, Calif. 92037. Meets the first Wednesday of each month Sept. through June at the University Club.

San Francisco Radiological Society
Secretary-Treasurer, Dr. Robert L. Koch, 3838 California St., Suite 106, San Francisco, Calif. 94118.

Section on Radiology, California Medical Association
Secretary, Dr. William H. Graham, 630 East Santa Clara St., San Jose, Calif.

Section on Radiology, Medical Society of the District of Columbia
Secretary-Treasurer, Dr. Albert M. Zelna, 21 Masters St., Potomac, Md. 20854. Meets at Medical Society Library, third Wednesday of January, March, May and October at 8:00 p.m.

Section of Radiology, National Medical Association
Secretary, Dr. Ruby Brooks, Dept. Radiol., Veterans Adm. Hosp., P.O. Box 511, Tuskogee, Ala. 36083. Annual Meeting.

Section on Radiology, Southern Medical Association
Secretary, Dr. Mario A. Calonje, 1514 Jefferson Highway, New Orleans, La. 70121. Annual Meeting.

Section on Radiology, Texas Medical Association
Secretary, Dr. George F. Crawford, St. Elizabeth Hospital, Beaumont, Tex. Meets annually with the Texas Medical Association.

Society for Pediatric Radiology
Secretary-Treasurer, Dr. John P. Dorst, 601 N. Broadway, Baltimore, Md. 21205. Annual meeting: Washington Hilton Hotel, Washington, D.C., Sept., 19, 1976.

Society of Gastro-intestinal Radiologists
Secretary-Treasurer, Dr. John R. Amberg, University Hospital, 225 W. Dickinson St., San Diego, Calif. 92103.

Society of Nuclear Medicine
Secretary, Dr. E. James Potchen, Edward Mallinckrodt Institute of Radiology, 660 S. Euclid Ave., St. Louis, Mo. 63110. *Administrative Officer*, Mrs. Margaret Glos, 211 E. 43rd St., New York, N. Y. 10017. Annual Meeting.

South Bay Radiological Society
Secretary, Dr. Robert Mindalzun, Valley Radiologists, Inc., 100 O'Connor Dr., San Jose, Calif. 95128. Meets the 2nd Monday of each month at the Santa Clara County Medical Society Bldg., 700 Empey Way, San Jose, Calif.

South Carolina Radiological Society, Chapter of ACR
Secretary, Dr. George W. Brunson, 1406 Gregg St Columbia, S. C. Annual meeting (primarily business) in conjunction with the South Carolina Medical Association meeting in May. Annual fall scientific meeting at time and place designated by the president.

South Coast Radiological Society Chapter of ACR
Secretary-Treasurer, Dr. Richard T. Love, Santa Barbara Med. Clin., 215 Pesetas Lane, Santa Barbara, Calif. 93110. Meets fourth Tuesday of alternate months, Sept., Nov., Jan., March and May.

South Dakota Radiological Society, Chapter of ACR
Secretary, Dr. M. F. Petereit, 2416 S. Phillips, Sioux Falls, S. D. 57105. Meets in spring with State Medical Society and in fall.

Southern California Radiation Therapy Association
Secretary-Treasurer, Dr. Duane J. Gillum, 250 W. Pueblo St., Santa Barbara, Calif. 93105. Meets quarterly.

Southern Radiological Conference
Secretary-Treasurer, Dr. J. W. Maxwell, P.O. Box 2144 Mobile Ala. 36601.

Tennessee Radiological Society, Chapter of ACR
Secretary-Treasurer, Dr. Jerry W. Grise, Methodist Hosp., 1265 Union Ave., Memphis, Tenn. 38104. Meets annually at the time and place of the Tennessee State Medical Association meeting.

Texas State Radiological Society, Chapter of ACR
Secretary, Dr. Francis E. O'Neill, 1128 Nix Prof. Bdg., San Antonio, Tex. 78205.

The Fleischner Society
Secretary, Dr. E. Robert Heitzman, State University of New York Upstate Medical Center, Syracuse, N. Y. 13210. Annual Meeting:

Tri-State Radiological Society
Secretary, Dr. Thomas Harmon, St. Mary's Hosp., Evansville, Ind. 47750. Meets bimonthly on the third Wednesday at area Hospitals.

Upper Peninsula Radiological Society
Secretary, Dr. A. Gonty, Menominee, Mich. Meets quarterly.

Utah State Radiological Society, Chapter of ACR
Secretary-Treasurer, D. Michael Edson, Dept. Radiol., Valley West Hosp., 4160 West 3400 South, Granger, Utah 84120. Meets quarterly at Holy Cross Hospital.

Vermont Radiological Society, Chapter of ACR
Secretary, Dr. J. Lorimer Holm, R.R. #3, Barre, Vt. 05641.

Virginia Chapter of ACR
Secretary-Treasurer, Dr. Charles P. Winkler, 3500 Kensington Ave., Suite 2-A, Richmond, Va. 23221.

Washington, D. C., Chapter of ACR
Secretary-Treasurer, Dr. Robert M. Allen, 9312 Convento Terr., Fairfax, Va. 22030.

Washington State Radiological Society, Chapter of ACR
Secretary-Treasurer, Dr. Donald J. Hesch, 3216 N.E. 45th Place, Seattle, Wash. 98105.

West Virginia Radiological Society, Chapter of ACR
Secretary-Treasurer, Dr. Andrew W. Goodwin, II, 200 Med. Arts Bldg., Charleston, W. Va. 25301. Meets concurrently with annual meeting of West Virginia State Medical Society, other meetings arranged by program committee.

Westchester County Radiological Society
Secretary, Dr. Leonard Cutler, 16 Guion Place, New Rochelle, N. Y. 10802. Meets on second Tuesday of October, December, February and May.

Wisconsin Radiological Society, Chapter of ACR
Secretary-Treasurer, Dr. June Unger, Wood VA Hosp., Wood, Wis. 53193. Meets twice a year, May and September.

Wisconsin Society of Therapeutic Radiologists
Secretary, Dr. Alvin Greenberg, Radiother. Ctr., Univ. Hospitals, Madison, Wis. 53706. Meets quarterly.

Wyoming Radiological Society, Chapter of ACR
Secretary, Dr. Ross J. Collie, Box 96, Lander, Wyo. 82520. Meets in fall with State Medical Society and in spring on call of President.

Mexico, Puerto Rico and Central America

Asociación Costarricense de Radiología
Secretary, Dr. Rafael Umaña-Umaña, Apartado 8-5340, San José, Costa Rica.

Asociacón de Radiólogos de Centro America y Panamá. Comprising: Guatemala, El Salvador, Honduras, Nicaragua, Costa Rica and Panamá
Secretary-General, Dr. Francisco Miranbell Solis, Apartado 3352, San José, Costa Rica, Central America. Meets annually in a rotating manner in the six countries.

Sociedad de Radiología de Salvador
Secretary, Dr. Carlos Meijia, 5a Av. Nte. No. 434, San Salvador, Rep. El Salvador.

Sociedad de Radiología de Guatemala
Secretary, Dr. Carlos E. Escobar, 9^2, Calle A 0-05, Zona 1, Guatemala

Sociedad Mexicana de Radiología, A.C.
Coahuila No. 35, México 7, D.F., México.
Secretary-General, Dr. Jorge Cano Coquí. Meets first Monday of each month.

Sociedad Radiológica Panameña
Secretary, Dr. L. Arrieta Sánchez, Apartado No. 6323, Panamá, R. de P. Meets monthly in a department of radiology of a local hospital chosen at preceding meeting.

Sociedad Radiológica de Puerto Rico
Secretary, Dr. César Rosa, Box 9387, Santurce, Puerto Rico 00908. Meets second Thursday of each month at 8:00 P.M. at the Puerto Rico Medical Association Bldg. in San Juan.

British Commonwealth of Nations

Association of Radiologists of the Province of Quebec
121 Boul. Taschereau, Greenfield Park, P. Q., Canada. Meets four times a year.

British Institute of Radiology
Honorary Secretaries, D. H. Traspnell, M. Cohen, 32 Welbeck St., London, W1M/7PG, England.

Canadian Association of Physicists, Division of Medical and Biological Physics
Honorary Secretary-Treasurer, Dr. R. G. Baker, Ontario Cancer Foundation, Ottawa Civic Clinic, 1053 Carling Ave., Ottawa 3, Ont., Canada.

Canadian Association of Radiologists
Honorary Secretary, Dr. Ross O. Hill, Suite 806, 1440 St. Catherine St. West, Montreal 107, Que., Canada. Annual Meeting:

Edmonton and District Radiological Society
Secretary, Dr. L. A. Koller, Suite 360, Professional Bldg., 10830 Jasper Ave., Edmonton 15, Alberta, Canada. Meets third Thursday of each month October to May, except December, at various Edmonton Hospitals.

Faculty of Radiologists
Honorary Secretary, P. D. Thomson, 28 Portland Pl., London, W1N 4DE.

Montreal Radiological Study Club
Secretary, Dr. W. Paul Butt, Montreal General Hospital, Montreal, Que., Canada. Meets first Tuesday evening, October to April.

Section of Radiology of the Royal Society of Medicine (Confined to Medical Members)
Meets third Friday each month at 8:15 p.m. at the Royal Society of Medicine, 1 Wimpole St., London, W. 1 M8AE, 1 England.

Société Canadienne-Française de Radiologie
Secretary-General, Dr. Hubert Sasseville, Verdun Hospital, Montréal, P. Q., Canada. Meets every third Tuesday from October to April.

The Hospital Physicists' Association
Honorary Secretary, J. B. Massey, B.Sc., Christie Hosp. and Holt Radium Institute, Physics Department, Withington, Manchester M20 9BX, England.

Toronto Radiological Society
Secretary, Dr. George Wortzman, Toronto General Hosp., Toronto 12, Ont., Canada. Meets second Monday of each month, September through May.

The Royal Australasian College of Radiologists
Honorary Secretary, Dr. T. P. Loneragan, 45 Macquarie St., Sydney, N.S.W. 2000, Australia.

South America

Colégio Brasileiro de Radiologia
Secretary-General, Dr. José Marcos Pires de Oliveira, Caixa Postal 5984, São Paulo, Brazil.

Federación Argentina de Sociedades de Radiología
Branches of the Federation are: Sociedad de Radiólogos de la Provincia de Córdoba; Sociedad Argentina de Radiología; Asociación Argentina de Radiología; Sociedad de Radiología, Radioterapéutica y Medicina Nuclear de Rosario; Sociedad de Radiología y Medicina Nuclear del Centro y Sudeste de la Provincia de Buenos Aires (Mar del Plata); Sociedad Salteña de Radiología y Medicina Nuclear; Sociedad de Radiología de Tucumán; Sociedad de Radiologia del Nordeste Argentino; Sociedad de Radiología de La Plata; and Sociedad de Radiología de San Juan.
Secretary-General-Treasurer, Dr. Roberto Habichayn, Av. Colón 637, Córdoba, Argentina.
Congress will be organized by Sociedad de Radiología, Radioterapéutica y Medicina Nuclear de Rosario in 1975.

Sociedad Argentina de Radiología
Secretary-General, Dr. Alba de la Torre, Santa Fé 1171, Buenos Aires, Argentina. Meets first Wednesday evening, April through December.

Sociedad Boliviana de Radiología
Secretary, Dr. Javier Prada Méndez, Casilla 1182, La Paz, Bolivia. Meets monthly. General assembly once every two years.

Sociedade Brasileira de Radiologia
Secretary, Dr. Armando Rocha Amoédo, Caixa Postal 1532, Rio de Janeiro, Brazil. General Assembly meets every two years in December.

Sociedade Brasileira de Radioterapia
Luiz Antonio, 644, São Paulo, Brazil. Meets monthly on second Wednesday at 9:00 p.m. in São Paulo at Av. Brigadeiro Luiz Antonio, 644.

Sociedad Chilena de Radiología
Secretary, Dr. Manuel Neira, Casilla 13426, Santiago, Chile. Meets first Friday of each month at Av. Santa María 1810 at 7:00 p.m.

Sociedad Colombiana de Radiología
Secretary-General, Dr. Gustavo Sánchez Sánchez, Bogotá, Colombia. Meets last Thursday of each month.

Sociedad Ecuatoriana de Radiología
Secretary, Dr. Luis Blum, Casilla 3712, Guayaquil, Ecuador.

Sociedad Paraguaya de Radiología
Secretary, Dr. Hugo Volpe Rios, 15 de Agosto 322, Asunción, Paraguay.

Sociedad Peruana de Radiología
Secretary-General, Dra. Ladis Delpino, Av. General Santa Cruz No. 315, Miraflores, Lima, Perú, Casilla Correo, 2306, Lima, Perú. Meets monthly except during January, February, and March.

Sociedad de Radiología del Atlantico
Secretary, Dr. Raul Fernandez, Calle 40 #41-110, Baranquilla, Colombia. Society meets monthly at the Instituto de Radiología.

Sociedad de Radiología del Nordeste Argentino
Secretary-General, Dr. Francisco J. Velar, Catamarca 561, Corrientes, Argentina.

Sociedad de Radiología de La Plata
Secretary, Dr. Hiram D. Haurigot, Calle 50 No. 374, La Plata, Argentina.

Sociedad de Radiología, Cancerología y Física Médica del Uruguay
Secretary-General, Dr. Manuel Gonzáles Maseda, Av. Agraciada 1464, piso 13, Montevideo, Uruguay.

Sociedade de Radiologia de Pernambuco
Secretary, Dr. Manoel Medeiros Instituto de Radiologia da Faculdade de Medicina da Universidade do Recife, Caixa Postal 505, Pernambuco, Brazil.

Sociedad de Roentgenología y Medicina Nuclear de la Provincia de Córdoba
Secretary-General, Dr. Lucas C. Di Rienzo, Ave. Grl. Paz. 151, Córdoba, Argentina.

Sociedad de Radiología, Radioterapéutica y Medicina Nuclear de Rosario
Secretary-General, Dr. Federico Frágola, Santa Fe 1798, Rosario, Argentina.

Sociedad Salteña de Radiología y Medicina Nuclear
Treasurer, Dr. Julio Luis Baldi, Av. Sarmiento 536, Salta, Argentina.

Sociedad Venezolana de Radiología y Medicina Nuclear
Secretary-General, Dr. Salvador Itriago Borgas, Apartado Postal 9213, Candelaria, Caracas, Venezuela. Meets monthly, third Friday at Colegio Médico del Distrito Federal, Caracas.

Continental Europe

Österreichische Röntgen-Gesellschaft
Secretary, Dr. Ernst Kotcher, Wiener Allgemeine Poliklinik Mariannengasse 10, A-1090 Wien, Austria. Meets second Tuesday of each month in Allgemeine Poliklinik.

Société Royale Belge de Radiologie
General Secretary, Dr. Joseph Baeyens, Alost, Belgium. Meets in February, March, May, June, September, October, November and December.

Société Européenne de Radiologie Pédiatrique
Secretary, Dr. J. Corbaton, Clinica Infantil "La Paz," Av. Generalissimo, 117 Madrid 34, Spain. Annual Meeting:
Permanent Secretary, Clément Fauré, Hôpital des Enfants Malades, 149, rue de Sèvres, 75 730, Paris Cadet 15, France.

Société Française de Radiologie Médicale, Médecine Nucléaire et Électrologie, and its branches: Société du Sud-Ouest, du Littoral méditerranéen, du Centre et Lyonnais, du Nord, de l'Ouest, de l'Est, du Massif Central, d'Outre-Mer et d'Étranger. Parent Society meets third Monday of each month, except during July, August and September, rue de Seine 12, Paris, France.
Secretary-General, Dr. Ch. Proux, 9 rue Daru, Paris 75008, France.

Société Française de Neuroradiologie
Secretary-General, Professeur agr. R. Djindjian 16, rue de l'Université 75, Paris 7ᵉ, France. Annual meeting.

Československá Radiologická Společnost
Secretary, Associate Professor Jaromír Kolář, M.D., Sc.D., Radiological Clinic, Praha 2, U nemocnice 2, Czechoslovakia. Meets monthly except during July, August and September. Annual general meeting.

Deutsche Röntgengesellschaft
President, Professor Dr. med. Walter Frommhold, Director of Medizinisches Strahleninstitut der Universität Tübingen, Röntgenweg 11, 7400 Tübingen, Germany.

Faculty of Radiologists of the Royal College of Surgeons in Ireland
Honor. Secretary, Max. J. Ryan, St. Stephen's Green, Dublin 2. Annual Meeting:

Società Italiana di Radiologia Medica e Medicina Nucleare
Administrative Secretary, Prof. E. Conte, Ospedale Mauriziano, 10128 Torino, Italy. Meets annually.

Societas Radiologica Danica
Secretary, Dr. Bent Langenfeldt, Tretommervej 20a, DK. 8240 Risskov, Denmark.

Nederlandse Vereniging voor Radiologie
Secretary, Dr. J. D. Mulder, Dept. of Rad., Akademisch Ziekenhuis, Leiden, Netherlands.

Norsk Forening for Medicinsk Radiologi
General Secretary, Gunnar Stake, Rikshospitalet, Oslo, Norway.

Scandinavian Radiological Society
Secretary-General, Professor C. F. Unnérus, M.D., Hagalung-Tapiola, Havsvindsvägn 5 C., Finland. Annual Meeting.

Sociedad Española de Radiología y Electrología Médicas y de Medicina Nuclear
Secretary-General, Dr. Pilar Gallar Barberá, Villanueva, 11, Madrid 1, España. Meets every other Saturday evening of each month, Oct. to June, inclusive, in Madrid.

Sociedade Portuguesa de Radiologia e Medicina Nuclear
Secretary-General, Dr. Luís Aires de Sousa, Av. Elias Garcia, 123- 1, Esg.-Lisboa i-Portugal.

Svensk Förening för Medicinsk Radiologi
Secretary, Dr. Hanz Ringertz, Röntgendiagnostika Avdelningen, Karolinska Sjukhuset 104 01 Stockholm 60, Sweden.

Schweizerische Vereinigung für Radiologie, Nuklearmedizin und Strahlenbiologie (Association Suisse de Radiologie, Médecine Nucléaire et de Radiobiologie)
Secretary, Dr. med. Gustav Schoch, Bethesdaspital, Gellerstrasse 144, 4000 Basel, Switzerland.

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Asia

Bengal Radiological Association
Honorary Secretary, Dr. B. Chatterji, 262 Rash Behari Ave., Calcutta 700019, India. Meets 1st Fri. and 3rd Wed. of every month.

Indian Radiological Association
Honor. Gen. Secretary, Dr. S. P. Aggarwal, 10-B Kasturba Ghandi Marg, New Delhi iioooi. 28th Indian Congress of Radiology will be held in Hyderabad in 1975.

Indonesian Radiological Society
Secretary, Dr. Gani Iljas Sasmitaatmadja, Radiology Dep., Faculty of Medicine, University of Indonesia, Salemba 6, Jakarta, Indonesia.

Iranian Radiological Society
Secretary, Dr. Majid Rooholamini, P.O. Box No. 14-1151, Teheran, Iran. The Society meets on the second Saturday of each month.

Israel Radiological Society
Secretary, Dr. M. A. Lerner, Hesharon Hosp., Petah-Tigva, Israel.

Philippine College of Radiology
Secretary-Treasurer, Dr. Eduardo V. Nievera, Box 1284 Commercial Center, Makati, Rizal D-708, Philippines. Meets every second Thursday of the month.

Radiological Society of Thailand
Secretary, Prof. Rojana Suvansuthi, M.D., Ph.D., Depart. of Rad., Sirizaj Hospital, Faculty of Medicine, Mahidol University, Bangkok 7, Thailand.

Africa

Association of Radiologists of West Africa
Honorary Secretary, C. A. Beetlestone, M.B., B.S., D.M.R.D., Dept. Radiol., University College Hosp., Ibadan, Nigeria.

Radiological Society of South Africa
Secretary, Dr. A. Visser, P. O. Box 8850, Johannesburg, South Africa.

South African International Radiological Congress
Director, Dr. Paul Sneider, P.O. Box 4878, Johannesburg, South Africa.

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ABSTRACTS OF RADIOLOGIC LITERATURE

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ROENTGEN DIAGNOSIS

Genitourinary System

Owman, T. Renal angiomyolipoma versus renal carcinoma: is an angiographic differential diagnosis possible? *Fortschr. a. d. Geb. d. Röntgenstrahlen u. d. Nuklearmedizin*, Sept., 1974, *121*, 315–320. (Address: Universitetsklinikernas Röntgendiagnostiska Central., Lasarettet, Lund, Sweden.)

It has been suggested in previous reports that angiographic differentiation between renal neoplasm and renal angiomyolipoma can be made. The author collected five cases of angiomyolipoma and compared the angiographic findings with 30 malignant renal tumors he had seen and with reports in the literature of 51 other malignant tumors.

The following characteristics have been considered characteristic of malignant renal tumors: superficial distribution of wide tortuous vessels; peripheral hypervascularity; aneurysms and pseudoaneurysms; normal interlobar arterial supply to areas of neovascularity; onion-peel or whorled appearance in the venous phase; large regions of avascularity; slow circulation through the mass; tumor vessels; and absence of arteriovenous shunts. Among his 30 patients with malignant tumors and his five patients with angiomyolipoma, the author found all of these characteristics except the neovascular regions supplied by a normal interlobar artery and the onion-peel or whorling in the venous phase, and these characteristics were found in neither the malignant tumors, nor the angiomyolipomas. The other characteristics were found in both.

The conclusion is, therefore, that in most cases of angiomyolipoma it will be impossible to exclude the malignancy on the basis of angiography alone.—*E. F. Lang, M.D.*

Cremin, B. J. Urinary ascites and obstructive uropathy. *Brit. J. Radiol.*, Feb., 1975, *48*, 113–117. (From: Department of Radiology, Red Cross Children's Hospital, University of Cape Town, South Africa.)

Neonatal ascites is recognized by abdominal distention, with gas filled loops of intestine floating in a diffusely opaque background. During a seven year period in Cape Town, South Africa in one hospital there were seen nine infants under the age of three months who required excretory urography for gross abdominal distention due to ascites. In two of these the urograms were normal and these patients suffered from sepsis and hemolytic disease. In the other seven there were five with posterior urethral valve obstruction, one with a large ureterocele on the left which obstructed both the bladder outlet and the right ureter, and one case of stricture following circumcision.

The exact site of origin of the ascites is not clear but in these patients rupture apparently occurred at the caliceal fornix and the roentgenograms showed an opaque halo about both kidneys. Previously this has been described as the "P" sign to include the kidney and ureter, but in these patients only the "O" sign was observed as there was no periurethral extension. The extravasated urine collects under the perirenal fascia, part of it passes through the peritoneum, and part of the fluid in the abdomen is peritoneal exudate.

Although posterior urethral valves are the commonest cause of obstruction in the neonatal urinary tract, obstruction at the ureteropelvic junctions also occurs and leads to hydronephrosis, although rupture and ascites usually do not occur.

The author describes the obstruction in the posterior urethra as due to a single structure forming a curtain which bulges into the urethra like a wind-filled spinnaker sail, and the concept of a single membrane is important because of the possibility of more simple division of the obstruction under roentgenologic control.

Although the prognosis for obstruction due to posterior urethral valves has improved, those infants presenting with urinary ascites have a poor outlook and there was only one survivor among these five cases.—*E. Frederick Lang, M.D.*

Skeletal System

Brashear, H. Robert, Jr., Venters, George C., and Preston, Edwin T. Fractures of the neural arch of the axis: report of twenty-nine cases. *J. Bone & Joint Surg.*, Oct., 1975, *57*-A, 879–887. (Address: H. Robert Brashear, Jr., M.D., University of North Carolina School of Medicine, Chapel Hill, North Carolina 27514.)

Fracture through the interarticular portion of the neural arch of the axis (hangman's fracture, traumatic spondilolisthesis) most often results from hyperextension of the neck or hyperextension plus longitudinal compression. In a study of 29 patients, all but one treated at North Carolina Memorial Hospital, 24 sustained the injury in vehicular accidents and only five in falls.

If the annulus and longitudinal ligaments are disrupted, the body of the second vertebra may flex and sublux forward on the body of C3, giving the roentgen appearance of a flexion injury. In these patients, anterior spur formation fuses the bodies of C2 and C3. Follow-up films showed solidly healed neural arch fractures in 26 with probable healing in two others. In only one did roentgenograms suggest nonunion of the fracture five years after injury, and in this case there was fusion between C2 and C3 with good clinical results. Three-quarters of the patients showed spontaneous anterior spur formation, interbody fusion, or both, between C2–3; in the 28 patients with flexion-extension films there was no evidence of instability.

Neurologic findings were few and there were no serious permanent neurologic defects. It is recognized that in instances of significant spinal cord injury at this high level, patients may not survive long enough to reach the hospital.

Treatment of the majority of patients was skeletal traction for six weeks followed by application of a Minerva cast or four-poster brace for an additional two to three months. To aid in reduction of the neural arch fracture, the head should be allowed to displace backward on the neck. Six patients were treated surgically, three by posterior fusion of C1 and C3, one posterior fusion of C2 and C3, one by fusion from occiput to C3, and one by anterior interbody fusion. One posterior fusion was considered inadequate and traction was required after surgery.

Follow-up films showed solid healing of the neural arch fractures in all, and every patient with posterior fusion had spontaneous interbody fusion or fusion of the anterior spurs. Since each patient in this series had a stable spine when healing was complete, the authors believe that surgical intervention is seldom necessary in this injury.—*Lois Cowan Collins, M.D.*

TAUSCH, G., SIEGMETH, W., and EBERL R. Generalisierte sekundäre Amyloidose bein chronischer Polyarthritis. (Generalized secondary amyloidosis in chronic polyarthritis.) *Wien. klin. Wchnschr.*, Sept., 1975, *87*, 521–524. (Address: Dr. G. Tausch, Krankenhaus der Stadt Wien-Lainz, Wolkersbergenstrasse 1, A-1130, Wien, Austria.)

In chronic rheumatoid arthritis, roentgen changes of the joints have usually far advanced so that associated complications may be given but little attention. Nevertheless, a formidable secondary amyloidosis occurs more frequently than is generally realized.

The diagnosis of secondary amyloidosis can be readily ascertained with the aid of a rectal biopsy which should also include tissue from the submucosa. Indications for such procedure include: (1) persistent or recurring proteinuria; (2) a progressive course of the rheumatoid arthritis with marked inflammatory activity; and (3) a duration of the disease for more than two years, with a marked tendency toward joint destruction. A congored stain of the obtained tissue as seen under polarized light readily confirms the histologic diagnosis of secondary amyloidosis.

In 80 of 177 selected patients, a rectal biopsy proved positive for secondary amyloidosis. Sixty-six of these had persistent proteinuria, while in additional 54 patients with proteinuria proved negative for amyloidosis. In a follow-up study of 66 patients with a positive biopsy, 16 had died with signs of uremia and secondary amyloidosis of the kidneys, the liver, the spleen and the adrenals.

While proteinuria can be temporarily absent, other signs of amyloidosis include a nephrotic syndrome, decreased renal function, increased sedimentation rate, and repeated infections.

There is no specific treatment for the amyloidosis. On the other hand, a survival rate of up to five years can be expected.—*Ernest Kraft, M.D.*

RÜCKERT, K. F., and BRINKMANN, E. R. Ermüdungsbrüche der Fersenbeine bei Soldaten der Bundeswehr. (Fatigue fractures of the calcanei in soldiers of the federal forces.) *München. med. Wchnschr.*, April, 1975, *117*, 681–684. (Address: Dr. med. K. F. Rüchert, D-2903 Bad Zwischenahn, Elmendorferstrasse, Germany.)

Fatigue fractures have frequently been observed among young recruits, especially after marching. In the last 20 years, however, these fractures have significantly to the calcanei instead.

From 1969 until 1974, 203 such fractures have occurred among 103 patients. They often remain unrecognized or are mistaken for other conditions. As a result, the duration of the illness is unduly prolonged mostly due to improper management.

The reason for the shift from the metatarsals to the calcanei can be readily explained by the training the recruits nowadays receive because of motorization and mechanization of the armed forces. Whereas formerly prolonged marches have been the rule, the training has become more concentrated on jumping exercises from considerable height.

Practically all affected soldiers were less than 25 years old and had suffered from specific symptoms during the first three months of service. There was vague pain of the heel for one to two weeks, edema of the dorsal aspect of the calcaneus, also pressure pain laterally on compression above and below the insertion of the Achilles tendon. When the symptoms were neglected or ignored, the contralateral heel became eventually involved, as was the case in 50 percent of the patients. In 17 percent, only specific shoe supports had been requested.

Roentgen findings remain unremarkable in the beginning. Ten days after onset of symptoms, however, a linear zone of condensation develops parallel with the posterior epiphyseal line and perpendicular to the course of the trabeculae. In 30 percent of the cases, this condensation occurs more anteriorly in the subtalar region and is symmetrical in bilateral involvement. The roentgen changes can remain positive up to 30 weeks.

Therapeutically, simple immobilization is suggested for two weeks and restriction of sport activities for three to six weeks. Only very gradual increase of exercise should be allowed. Prophylactically, unilateral jumping should be avoided during the first six weeks of training.—*Ernest Kraft, M.D.*

DELBARRE, F., RONDIER, J., DELRIEU, F., EVRARD, J., CAYLA, J., MENKES, C. J., and AMOR, B. Pyogenic infection of the sacro-iliac joint: report of thirteen cases. *J. Bone & Joint Surg.*, Sept., 1975, *57*-A, 819–825. (Address: Dr. F. Delbarre, C. H. U. Cochin-Port Royal, Pavillon Ollier, 27 rue du Faubourg St.-Jacques, Paris 14, France.)

Thirteen patients were treated for pyogenic infection of the sacro-iliac joint at the Hospital Côchin, in Paris, France, during the past ten years. Criteria for diagnosis were: (1) unequivocal clinical and roentgenographic signs of sacro-iliac disease; (2) an organism isolated in fluid from the joint or on blood culture, or, if no organism found, the lesion was cured by antibiotic drug; and (3) negative serological reaction for Salmonella and Brucella. The results were compared with those of thirty-four cases reported in the literature.

Pyogenic sacro-iliac arthropathy is rare, and is exceeded in incidence by tuberculous infection and ankylosing spondylitis and Reiter's disease. Staphylococci are the organisms most frequently found, but other pyogenic organisms are found on occasion. No cases of typhoid or brucellar sacro-iliitis were recorded. In ten patients the probable source of infection was known: two skin infections, two buccopharyngeal infections, two osteomyelitis at distant sites, two postpartum infections and two urinary infections. The source of the infection was mentioned in 22 of the cases in the literature, and was considered to be pelvic in origin in 19.

Osteoblastic reaction occurred slowly. In four patients no such condensation appeared and these were patients who had been treated very intensively with antibiotics. Healed lesions showed synostosis in five patients, two of which were arthrodeses. Six patients had persistent erosions and in two the joint returned to normal appearance.

Treatment was immobilization and antibiotics. The three indications for surgery are: (1) uncertain diagnosis, (2) abscess formation, and (3) failure to respond to antibiotics. The indications for surgical ankylosis are: (1) if the microscopic findings suggest the possibility of tuberculosis; and (2) if destructive lesions are so extensive that it is unlikely they can be controlled by antibiotics alone.

Abscess formation is an absolute indication for surgery. In the three patients in whom this occurred, there was rapid cure without arthrodesis in all three. Prognosis is good for full recovery within about three months after onset of therapy.—*Lois Cowan Collins, M.D.*

GASTROINTESTINAL

FUCHS, W. A. and PREISIG, R. Prolonged drip-infusion cholangiography. *Br. J. Radiol.*, 1975, *48*, 539–544. (Address: University of Berne Medical School, Berne, Switzerland.)

Previous experimental work in animals has shown that the hepatic excretion of iodipamide and ioglycamide is subject to a transport maximum (TM). Doses in excess of this TM are largely excreted in the urine. In the present study the TM for man was estimated in three subjects with indwelling T-tubes: figures of 19–23 mg/minute for ioglycamide were obtained.

It was thought that prolonged administration of contrast at levels slightly above the TM might have advantages in patients with impaired liver function. In obstruction the gradual excretion of contrast could improve the chances of filling the ducts completely, while in hepato-cellular disease the gall bladder might have time to concentrate the contrast. Ioglycamide was therefore given by slow overnight infusion, equivalent to 35 mg/minute, to patients in whom standard cholangiography had been unsuccessful. The overall success rate was 75 percent with similar improvement in both obstructive and hepatocellular disease.—*Author's Abstract*

CARDIOVASCULAR

RÖSCH, J., GOLDMAN, M. L., and DOTTER, C. T. Experimental catheter obstruction of the gastric coronary vein, possible technique for percutaneous intravascular tamponade of the gastroesophageal varices. *Invest. Radiol.*, 1975, *10*, 206–211. (Address: University of Oregon Medical School, Portland, Oregon.)

Experimental catheter obstruction of the left gastric (coronary) vein was explored in 10 dogs. Using a transjugular approach, the liver was punctured and the portal vein catheterized. Coaxially introduced catheters were then used to catheterize selectively and produce an intravascular obstruction (tamponade) of the gastric coronary vein. Balloon catheters were used for a temporary occlusion. Injection of a tissue adhesive, isobutyl 2-cyanoacrylate, was used for a definitive obliteration. The achieved results show the anatomical feasibility of this approach and give good perspective for development of a clinical method for percutaneous intravascular tamponade of bleeding gastroesophageal varices in cirrhotics.—*Author's Abstract*

BARR, J. W., LAKIN, R. C., and RÖSCH, J. Vasopressin and Hepatic Artery, effect of selective celiac infusion of vasopressin on the hepatic artery flow. *Invest. Radiol.*, 1975, *10*, 200–205. (Address: University of Oregon Medical School, Portland, Oregon.)

Electromagnetic flow measurement study was performed in 20 anesthetized dogs to evaluate the effect of selective celiac infusion of vasopressin on the hepatic arterial vasculature. The hepatic arterial flow showed a biphasic response with an initial decrease followed by a substantial increase in spite of a continued infusion. The left gastric, splenic, and superior mesenteric arteries showed a monophasic response with persistent decrease of flow during the whole infusion. The biphasic response of the hepatic arterial flow is thought to be due to autoregulatory dilative action of the liver to a decrease of the portal flow. The results and previous clinical experience suggest that the selective infusions of vasopressin into arteries supplying the liver can be used for short-term vasoconstrictive therapy of acute gastrointestinal bleeding in patients without liver damage. Further experience is necessary to evaluate the safety of prolonged hepatic infusions in patients with liver disease.—*Author's Abstract*

BERGE, T., LEPASOON, J., and OLIN, T. Angiographic patterns of splenic lesions following blunt trauma, an experimental study in monkeys. *Invest. Radiol.*, 1975, *10*, 329–341. (Address: University Department of Pathology, General Hospital, Malmö, Sweden.)

Splenic angiography was performed before and after graded blunt trauma to the spleen in 15 monkeys. In 9 of these, follow-up angiography could be performed a week or more later. Pronounced spasm of the splenic artery and leakage of contrast medium into the peritoneal cavity were found to imply a serious prognosis. Local reversible spasm of arterial branches can cause transient defects in parenchymal filling. Larger defects corresponding to hematoma, extravasation of contrast medium, and displacement of vessels may be compatible with good primary prognosis. If, however, these signs indicate that the lesion is of sufficient magnitude and has a peripheral location there is a risk that extensive bleeding will occur. So-called "delayed rupture" never occurred in this study.—*Author's Abstract*

DAVIDSON, J. K., MORLEY, P., HURLEY, G. D., and HOLFORD, N. G. H. Adrenal venography and ultrasound in the investigation of the adrenal gland: an analysis of 58 cases. *Br.J. Radiol.*, 1975, *48*, 435–450. (Address: Department of Diagnostic Radiology and the M.R.C. Blood Pressure Unit, Western Infirmary, Glasgow G11 6NT, Scotland.)

Adrenal venography has been carried out in 58 patients with the left adrenal vein being successfully catheterized in 91 percent and the right in 77 percent.

Of the 30 patients with primary hyperaldosteronism, 11 adenomas (12–35 mm diameter) have been demonstrated at venography and two of 15 mm suspected, all of which were confirmed surgically. Aldosterone levels in the adrenal vein plasma were raised on the affected side. In the group of proved micronodular hyperplasia, two patients had surgically confirmed macronodules and venography demonstrated one of 12 mm diameter. Two adenomas of 11 mm and one macronodule of 15 mm have been demonstrated at venography in the remainder who have not had an operation.

Ultrasound was carried out in 12 patients with primary hyperaldosteronism, ten of which had tumors at venography. Two adenomas measuring 30 and 31 mm were outlined by ultrasound and confirmed surgically. Seven adenomas, including one macronodule (10–25 mm in diameter) were not defined. Three intra-adrenal phaeochromocytomas (45–90 mm) and one extra-adrenal (80–85 mm) were demonstrated at arteriography, identified by ultrasound and confirmed surgically.

Of the ten patients with Cushing's syndrome three had enlarged glands at venography, this was confirmed surgically.

Cumulative experience from this analysis and published reports indicate that venography will demonstrate tumors of 10 mm or more in diameter and outline enlarged glands; aldosterone assays will lateralize tumors as small as 3 mm; ultrasound will outline tumors of 30 mm and selective adrenal arteriography will demonstrate tumors of 10 mm.

One patient developed acute adrenal cortical insufficiency with intra-adrenal extravasation on one side and thrombosis of the central vein on the opposite side. A second case developed temporary adrenocortical insufficiency. Published reports indicate that the risk of complication is about 1 percent.

The report includes an anatomical study of the efferent adrenal veins in 50 patients paying particular attention to the diameter, number of accessory hepatic veins, angle of entry and position of the right adrenal vein.—*Author's Abstract*

CHEST

SHARMA, O. P. and GORDONSON, J. Pleural effusion in sarcoidosis: a report of six cases. *Thorax*, 1975, *30*, 95–101. (Address: University of Southern California School of Medicine, Los Angeles, California.)

Six (4 percent) of 150 patients with sarcoidosis had a pleural effusion. A review of the literature revealed seven more patients with pleural sarcoidosis. Analysis of the 13 patients reported so far did not reveal any clinical, radiological, or laboratory feature which may be of diagnostic significance. The diagnosis of pleural sarcoidosis was based on clinical or radiographic grounds and histological evidence of noncaseating granulomata. In three of the patients pleural fluid resolved spontaneously; the other three were treated with corticosteroids. It is suggested that pleural involvement in sarcoidosis, especially in Negroes, may be more frequent than is generally realized and that effusion may occur either at the time of initial presentation or later in the course of the disease.—*Author's Abstract*

Bachman, A. L. and Teixidor, H. S. The posterior tracheal band: a reflector of local superior mediastinal abnormality. *Br. J. Radiol.*, 1975, *48*, 352–359. (Address: Columbia University, New York, New York.)

The posterior tracheal band (PTB) is a thin band of uniform width consisting primarily of the posterior tracheal wall which is observed almost constantly in a well-positioned and exposed lateral view of the chest. It is formed by two interfaces; an internal junction line between the inner tracheal wall and air in the lumen, and an external junction line between the adventitial surface of the right posterior wall (with paper-thin mediastinal covering) and aerated lung in the right retrotracheal recess. Any pathological process in the mediastinum, pleura or right upper lobe medially which affects the external interface causes an alteration or disappearance of the PTB. Anatomical studies explaining the formation of the PTB and clinical cases illustrating its alteration or disappearance are presented.—*Author's Abstract*

Andrus, W. S., Hunter, C. H., and Bird, K. T. Remote interpretation of chest roentgenograms. *Chest*, 1975, *67*, 463. (Address: Dr. Bird, 275 Charles Street, Boston, Massachusetts 02114.)

A series of 98 chest films was interpreted by two physicians on the basis of monitor display of the transmitted television signal representing the roentgenographic image. The transmission path was 14 miles long, and included one active repeater station. Receiver operating characteristic curves were drawn to compare interpretations rendered on television view of the image with classic, direct view interpretations of the same films. Performance in these two viewing modes was found to be quite similar. When films containing only hazy densities lacking internal structure or sharp margins, were removed from the sample, interpretation of the remaining films was essentially identical via the two modes. Since hazy densities are visible on retrospective examination, interpretation of roentgenograms at a distance via television appears to be a feasible route for delivery of radiologic services.—*Author's Abstract*

Herman, P. G., Gerson, D. E., Hessel, S. J., Mayer, B. S., Watnick, M., Blesser, B., and Ozonoff, D. Disagreements in chest roentgen interpretation. *Chest*, 1975, *68*, 278. (Address: Harvard Medical School, Boston, Massachusetts 02115.)

Each of 100 chest radiographs selected randomly from a hospital population were read by five experienced radiologists. The films were rich in abnormal findings. Disagreement analysis was performed considering the entire content of the interpretation. The disagreements were graded by a panel as to type (false negative, false positive, and indeterminate) and significance. The overall repeatability of the panel's performance was 75 percent. Forty-one percent of the reports contained potentially significant errors and 56 percent indeterminate disagreements. Among all errors 78 percent were false negatives and 22 percent were false positives. The error rate varied among readers. An average of 25 percent of important findings were omitted by an individual reader. An association between specific abnormalities and the types of disagreement was found.—*Author's Abstract*

Kovnat, D. M., Rath, G. S., Anderson, W. M., Siber, F., and Snider, G. L. Bronchial brushing through the flexible fiberoptic bronchoscope in the diagnosis of peripheral pulmonary lesions. *Chest*, 1975, *67*, 179. (Address: Dr. Snider, VA Hospital, 150 South Huntington, Boston, Massachusetts 02130.)

Bronchial brushing was performed concomitantly with transnasal flexible fiberoptic bronchoscopy in 44 patients with localized peripheral pulmonary lesions and absence of visible bronchial abnormality down to subsegmental level. Fluoroscopic confirmation of brush placement was obtained. A diagnosis of malignancy was made by bronchial brushing in 12 of 23 patients (52 percent) proved to have neoplasm, although diagnostic accuracy rose to six of seven patients (86 percent) in the final quarter of the study. There was no relationship between diagnostic accuracy and tumor location. Diagnostic accuracy was highest for squamous cell carcinoma, intermediate for adenocarcinoma, and lowest for undifferentiated carcinoma. A diagnosis of tuberculosis was made in two of 21 patients found not to have malignancy, and bronchial brushing was the only procedure to yield diagnostic material in these two patients. There were no false-positive cytologic examinations and no complications. Fluoroscopic control of placement of the bronchial brush passed through the fiberoptic bronchoscope allows a single, high-yield, diagnostic procedure to be performed with minimal risk to the patient. In selected cases, thoracotomy may be avoided by this procedure.—*Author's Abstract*

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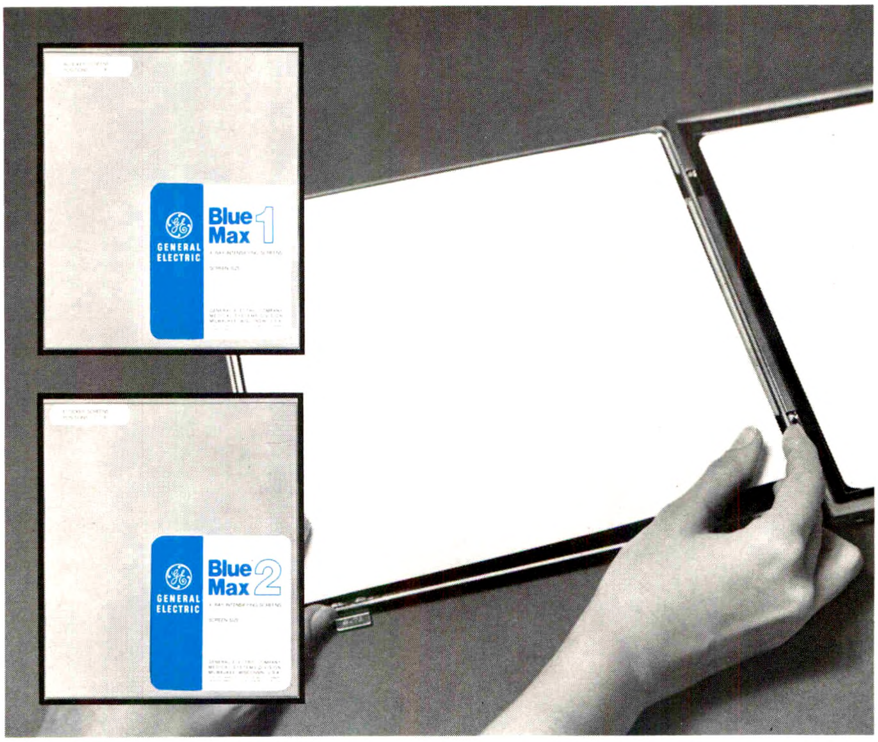

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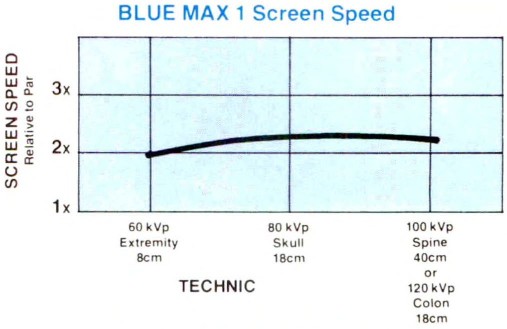
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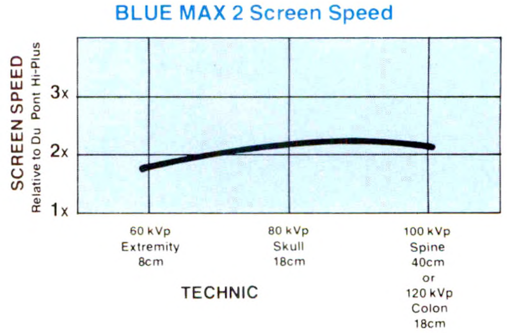
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At the Bayshore Inn (Western International Hotels), Vancouver

PROGRAM

Wednesday, May 19

Morning *Chest*

—Pulmonary Edema .... Robert G. Fraser.
—Diffuse Bilateral Pulmonary Disease in Children .... J. Scott Dunbar.
—Pleuropulmonary Changes in Non-penetrating Thoracic Trauma .... John G. Clement.
—Immunological Diseases of the Thorax .. Robert G. Fraser.
—Cyst and Cyst-like Lesions of the Lung in Children .. .. J. Scott Dunbar.

Afternoon *Skeletal*

—Iatrogenic Lesions of the Skeleton .... Ronald O. Murray.
—Some Interesting Aspect of Skeletal Trauma .... Harold G. Jacobson.
—Importance of Soft Tissue in Relation to Skeletal Radiology .... Ronald O. Murray.
—The Hand as a Mirror of Local and Systemic Diseases .... Harold G. Jacobson.

Film Reading Session:

Chairman: Harold G. Jacobson
Panelists: J. Scott Dunbar, Robert G. Fraser, Ronald O. Murray.

Thursday, May 20

Practical Techniques in Diagnostic Radiology

Morning

—Gastrointestinal Examination in Infants and Children .... J. Scott Dunbar.
—Non-Operative Removal of Common Duct Stones .... H. Joachim Burhenne.
—Angiographic Techniques in Control of Gastrointestinal Hemorrhage .... Josef Rösch.
—Peritoneography: Normal & Pathological Anatomy .... Morton A. Meyers.
—Genitourinary Examination in Neonates and Infants .. .. Walter E. Berdon.
—PANEL DISCUSSION.

Afternoon

—Techniques and Advances in Myelography .... Alan J. Fox.
—Percutaneous Biopsy of Lung, Kidney and Bone .... Anthony F. Lalli.
—Chest Radiography .... Robert G. Fraser.
—Equipment and Techniques in Abdominal and Obstetrical Ultrasound .... George R. Leopold.
—PANEL DISCUSSION.

Friday, May 21

Morning *Gastrointestinal Radiology*

—Diagnosis of Gallstones .... H. Joachim Burhenne.
—Seeded Metastases: Pathways and Diagnostic Features .... Morton A. Meyers.
—Abdominal (non-obstetrical) Ultrasonography .... George R. Leopold.
—Angiography of the Liver & Pancreas .... Josef Rösch.
—Anatomy of the Post-Op. Stomach .. H. Joachim Burhenne.
—Intestinal Effects of Pancreatitis ...... Morton A. Meyers.

Afternoon *Genitourinary Radiology*

—Controversies on Reflux, Infection and Pyelonephritic Scarring .... Walter E. Berdon.
—Renal Papillary Necrosis .... Anthony F. Lalli.
—Renal & Adrenal Angiography .... Josef Rösch.
—Obstetrical Ultrasonography .... George R. Leopold.
—Obstructive Uropathies .... Walter E. Berdon.
—Calculi and Calcifications of the Urinary Tract .... Anthony F. Lalli.

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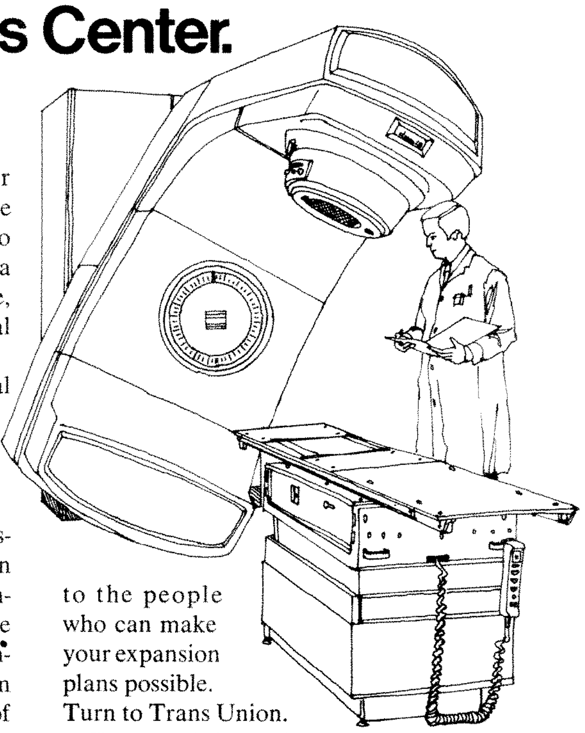

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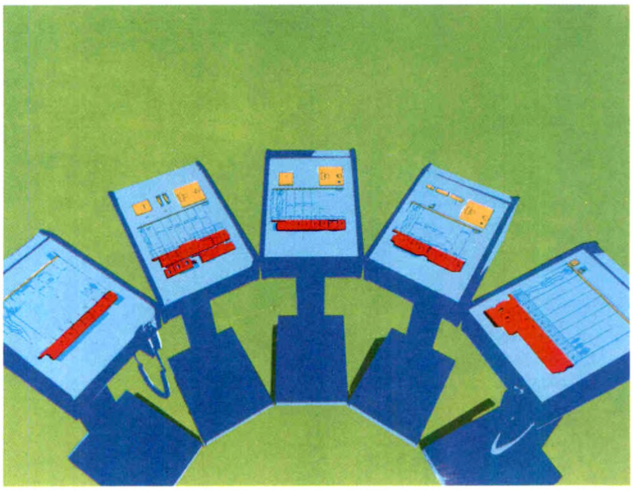

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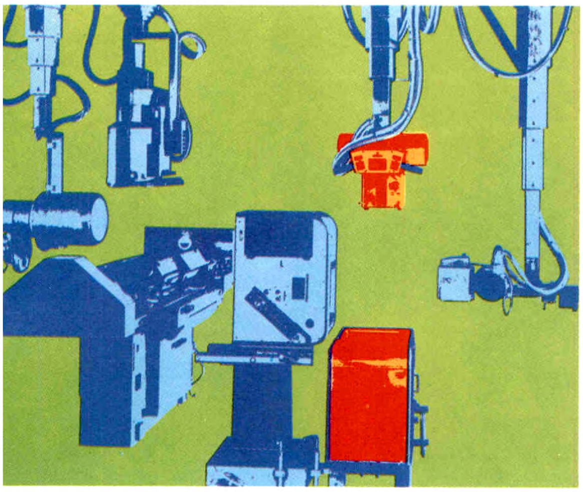

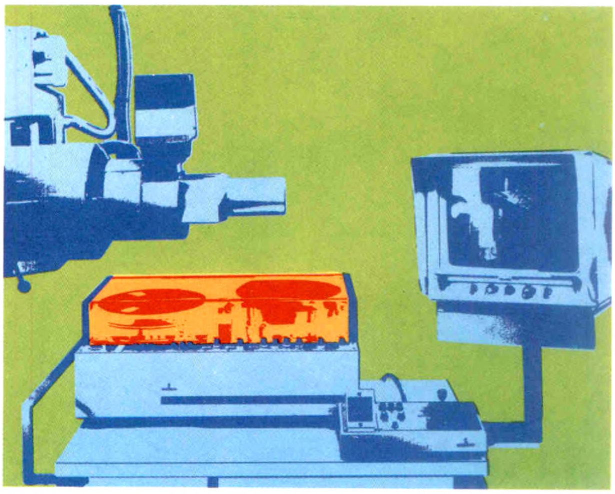

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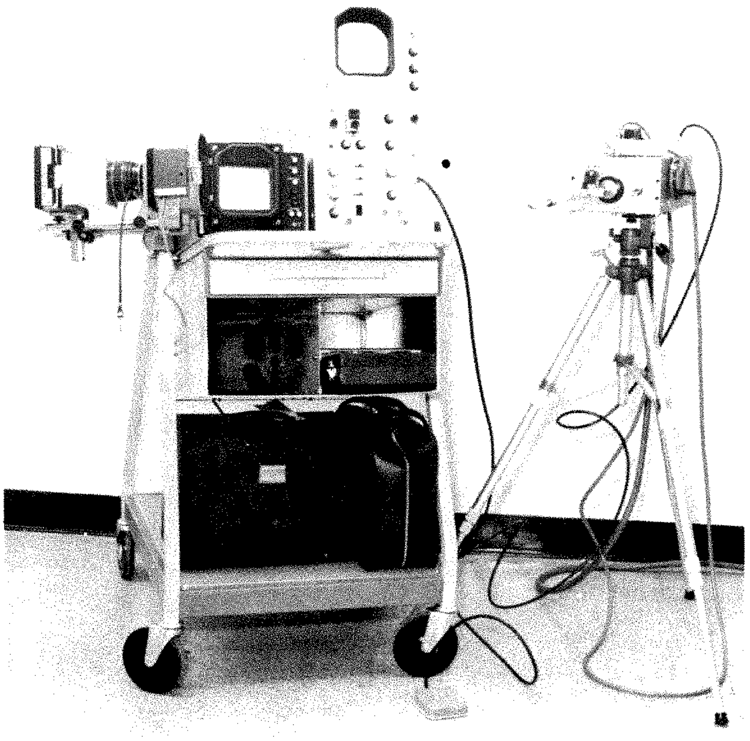

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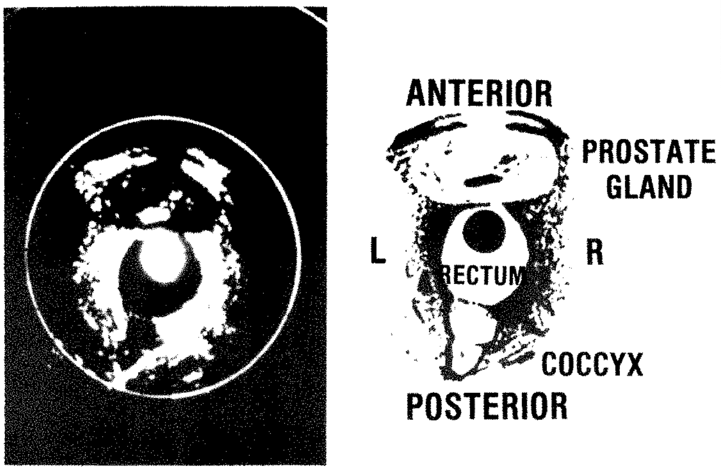

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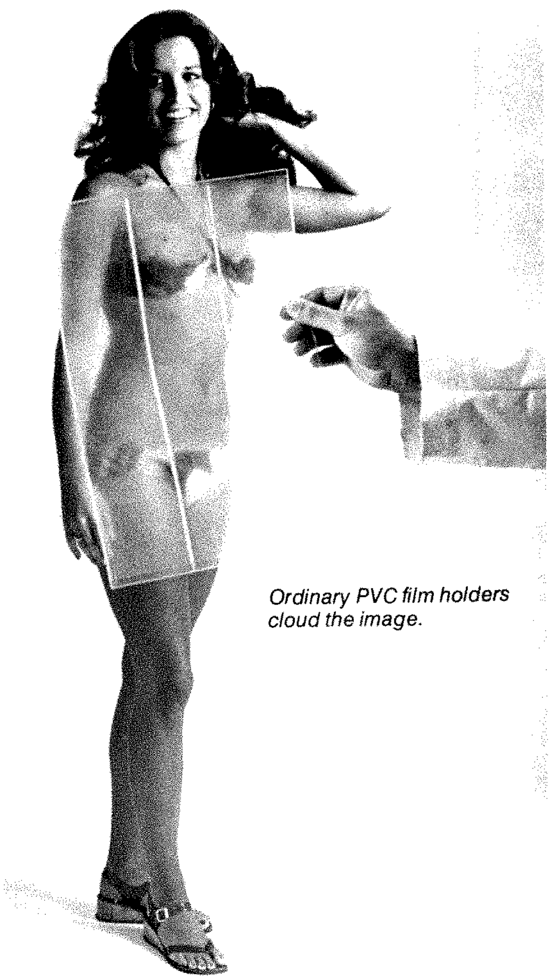

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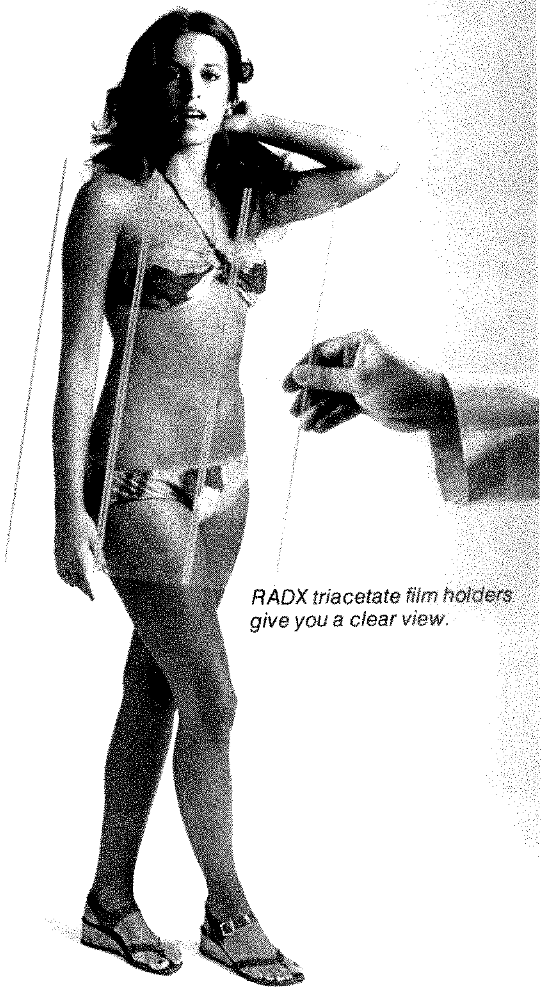

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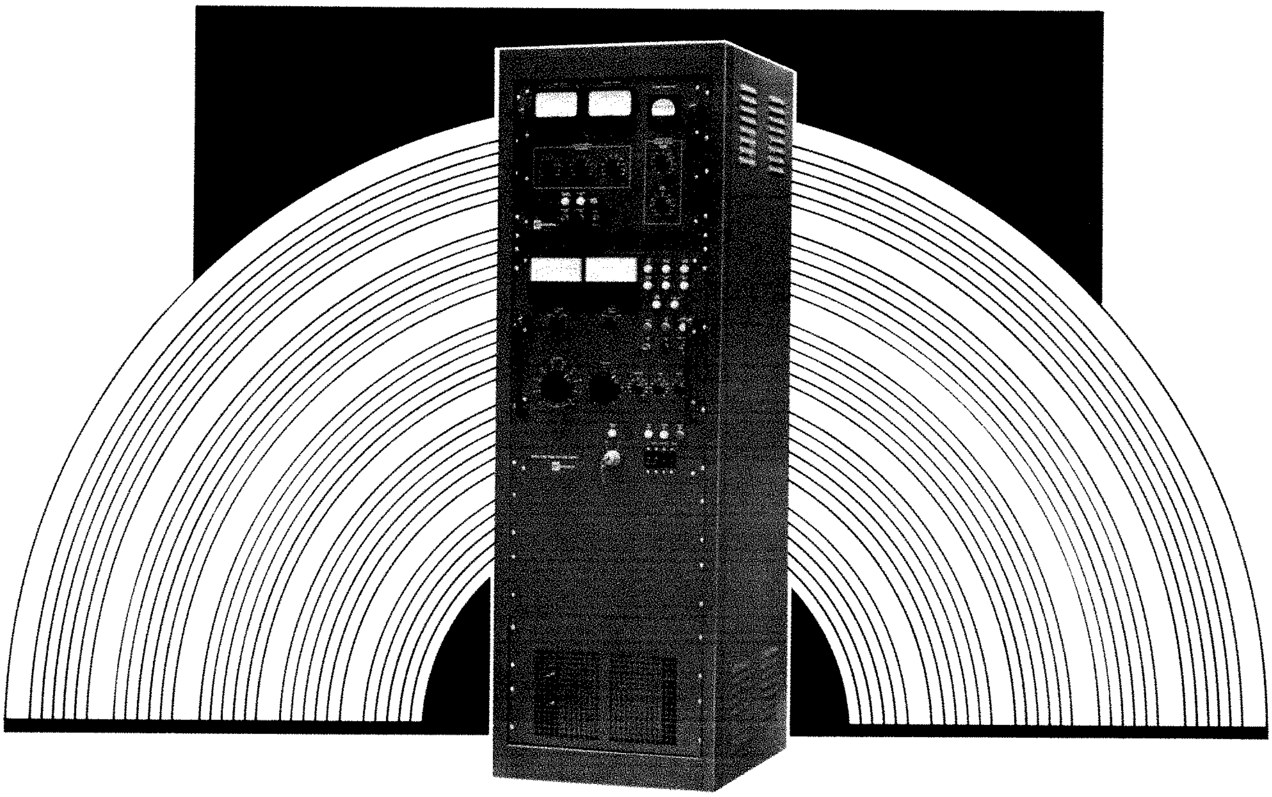

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ADMINISTRATION OF A RADIOLOGY DEPARTMENT: Hints for Day-to-Day Operation *by* **Murray L. Janower,** *St. Vincent Hospital, Worcester, Massachusetts.* To demonstrate that the application of common sense and sound business management principles to a radiology department will result in a marked improvement in its day-to-day operation is the purpose of this volume. Specific attention has been given to the methods used in handling patients, functions of the technologists, the establishment of a quality control program, efficient production of radiological reports, methods of film interpretation, darkroom operations, and functions of a file room. *'76, 72 pp., 8 il., 7 tables, $7.50*

XERORADIOGRAPHY OF THE BREAST (3rd Ptg.) *by* **John N. Wolfe,** *Hutzel Hospital, Detroit, Michigan. Foreword by* **Wendell G. Scott.** The mechanics and principles involved in this procedure are clearly defined. Breast anatomy and the normal breast are discussed, providing a thorough understanding necessary to achieve the proper technique and correct interpretation of the xeromammogram. An up-to-date discussion of benign conditions, miscellaneous conditions, and malignancies is presented. The xeroradiographs are accurately reproduced in their original blue color for consistency of detail. *'75, 194 pp. (8 1/2 x 11), 242 il. (92 in color), $23.50*

THE RENAL UPTAKE OF RADIOACTIVE MERCURY ($^{197}HgCl_2$): Method for Testing the Functional Value of Each Kidney, Technique—Results—and Clinical Application in Urology and Nephrology *edited by* **Claude Raynaud,** *Service Hospitalier Frederic Joliot, Orsay, France. Foreword by* **Pierre Royer.** *(41 Contributors)* The first chapters of this text describe several techniques of uptake measurement along with simplified systems of external counting, scanners or gamma cameras, and specific problems associated with the deep position of the kidney or Hg metabolism. The rest of the book discusses the normal values of Hg renal uptake and the results obtained in patients. *'76, 248 pp., 110 il., 47 tables, $22.75*

AN ATLAS OF POLYTOME PNEUMOGRAPHY *by* **Taher El Gammal** *and* **Marshall B. Allen, Jr.,** *both of Medical College of Georgia, Augusta. Assisted by* **Paul Dyken.** This atlas presents a large number of studies which supplement the study of normal anatomy of the cerebrospinal fluid pathways, and provides comparison for the identification of abnormal structures. Concentration is on the findings of polytome pneumography, but where possible correlations are made with angiography, positive contrast ventriculography, and CAT examinations. Relative values of these different examinations are demonstrated. *'76, 480 pp. (8 1/2 x 11), 729 il., $39.50*

ARTHROGRAPHY OF THE SHOULDER: The Diagnosis and Management of the Lesions Visualized *by* **Julius S. Neviaser,** *George Washington Univ., Washington, D.C.* Normal arthrograms are illustrated in this text, anatomical variations of a normal shoulder joint are described, and frequent and unusual lesions are discussed. Outlines of conservative and operative treatment principles are also presented. Individual chapters cover adhesive capsulitis, ruptures of the rotator cuff, ruptures following a dislocation or fracture, chronic and frequently misunderstood ruptures, lesions of the biceps tendon, dislocation of the shoulder, pathologic anatomy of old unreduced dislocations, and the "stripping operation." *'75, 288 pp., 265 il., $22.50*

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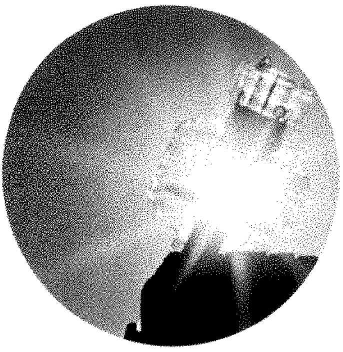

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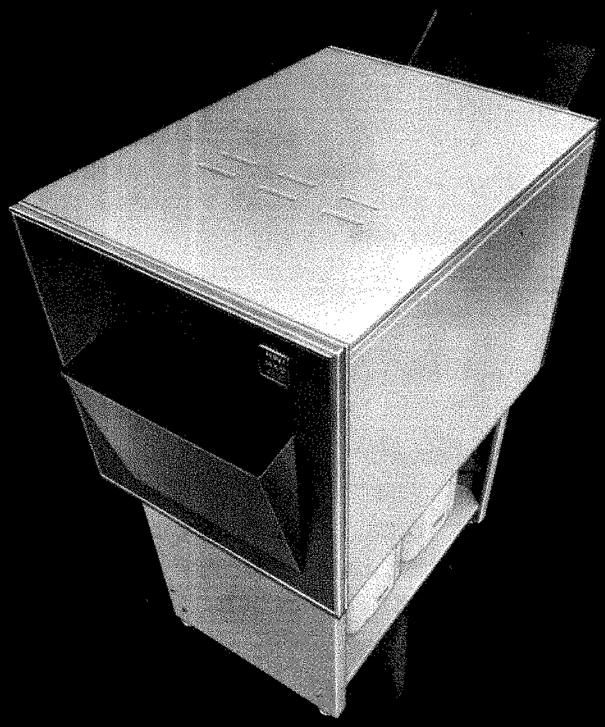

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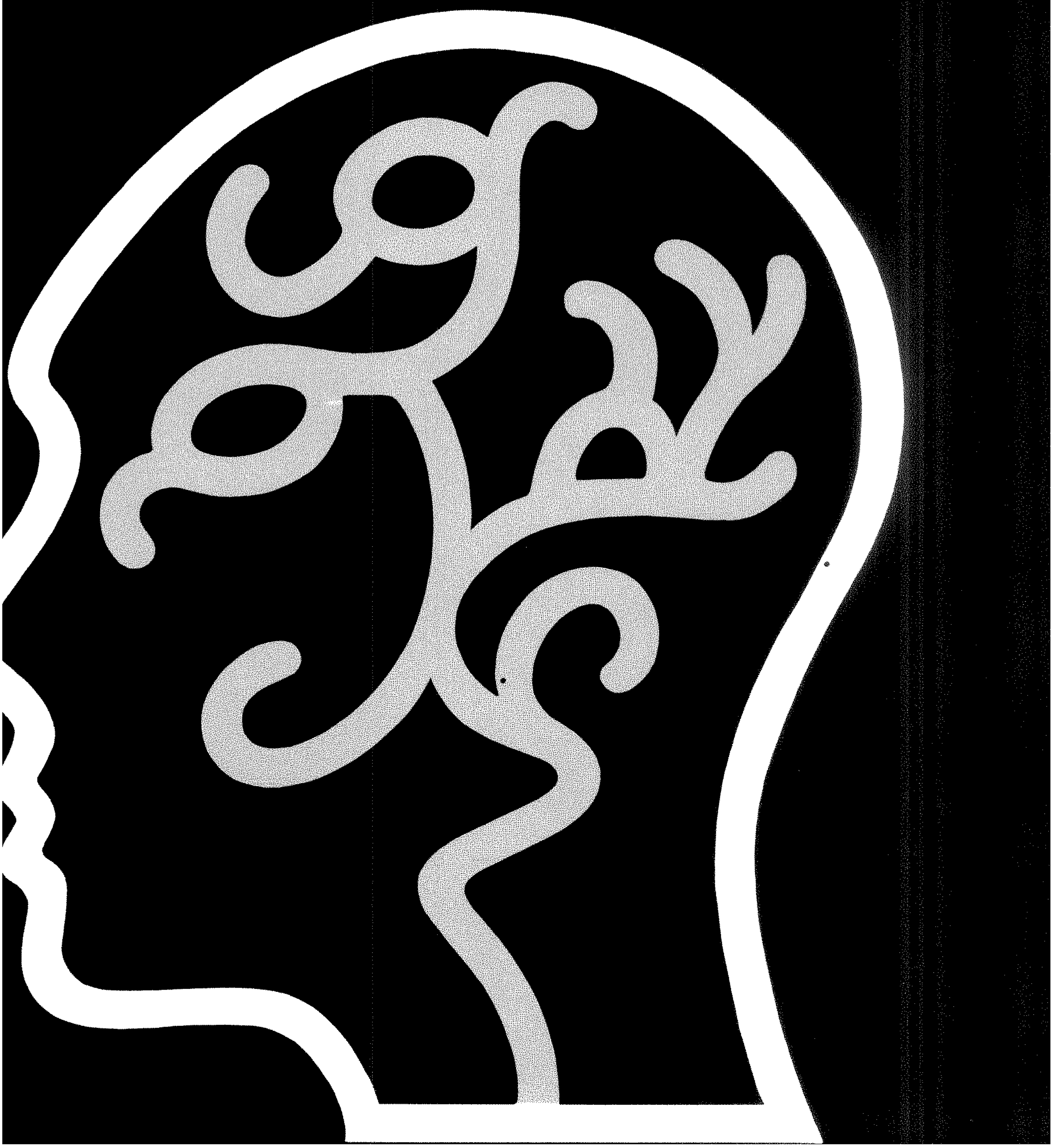

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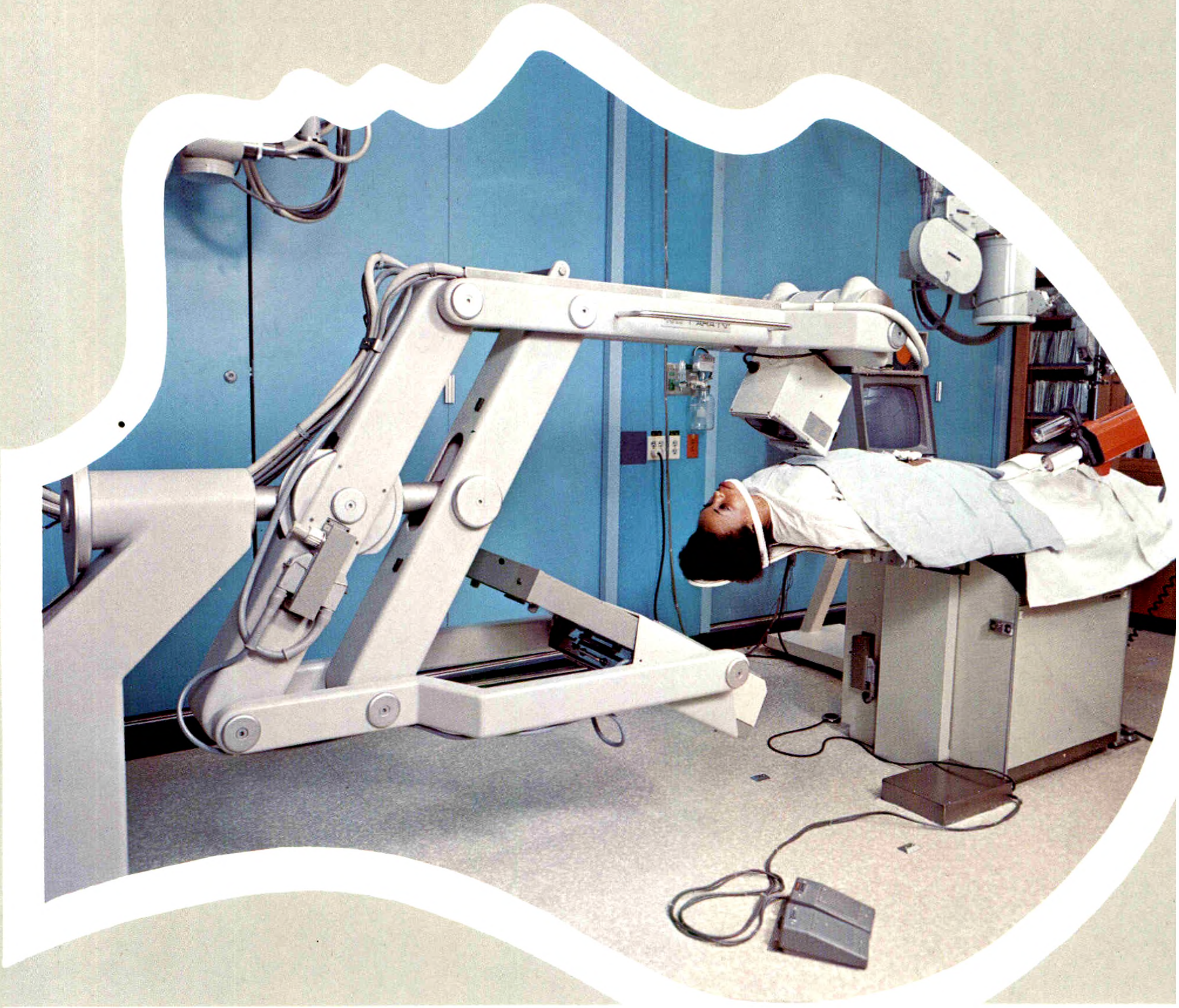

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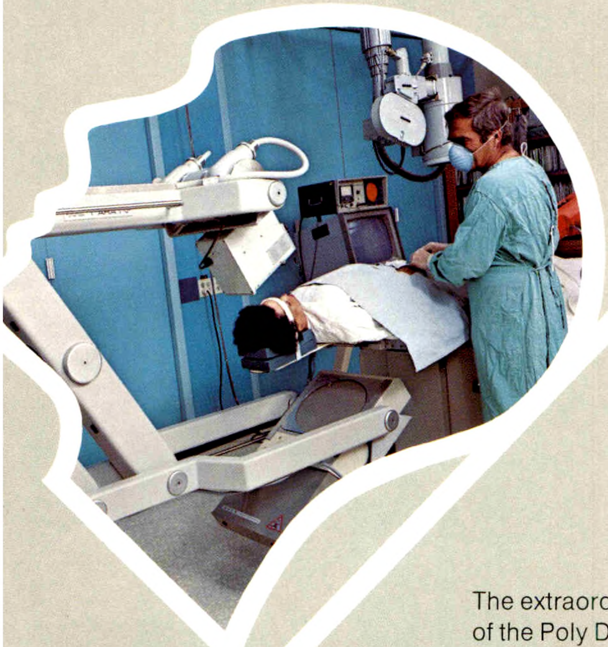

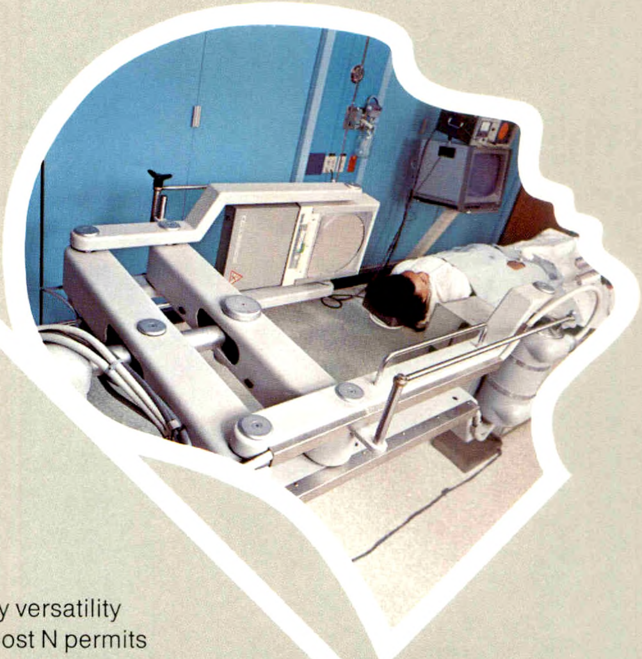

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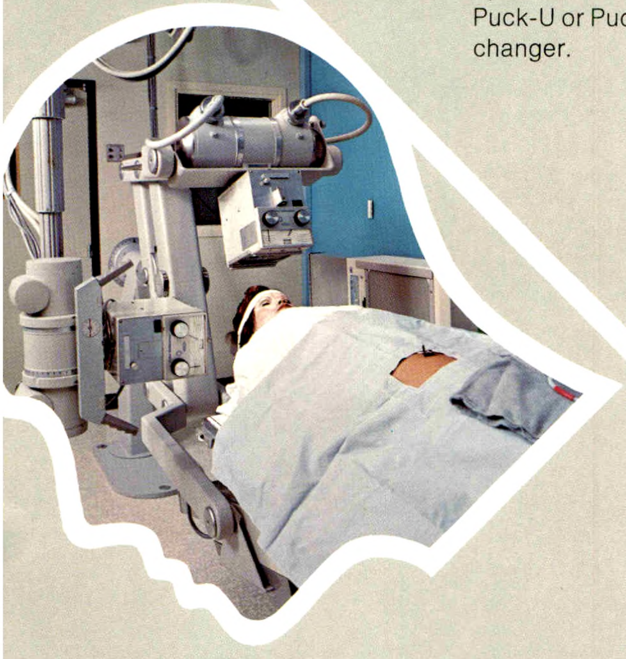

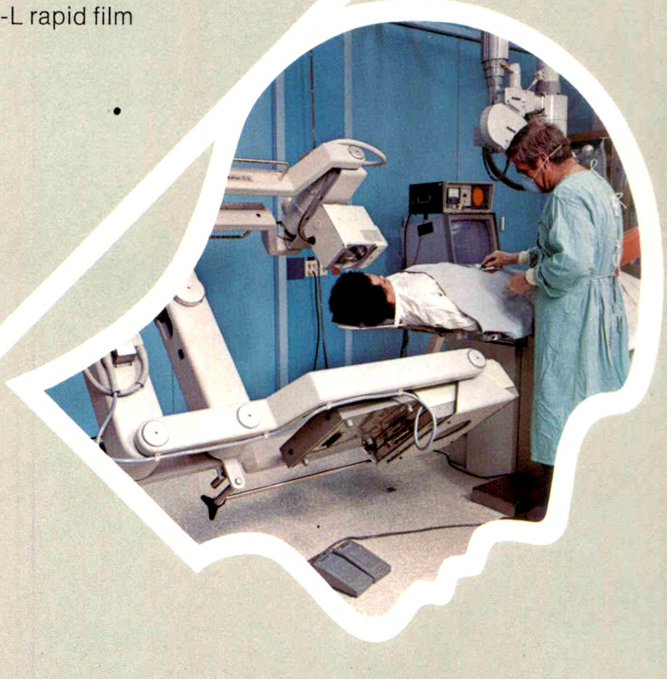

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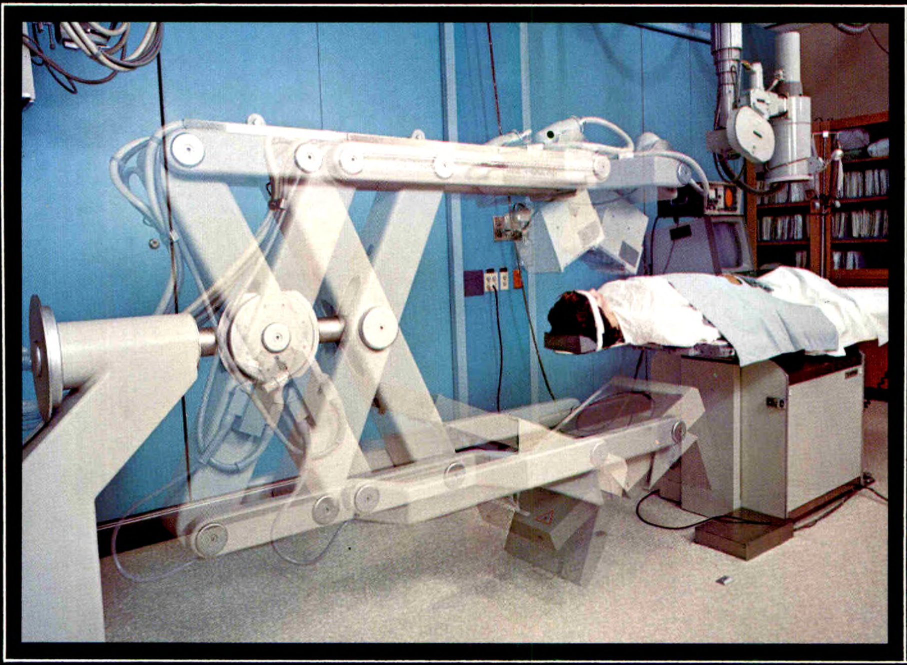

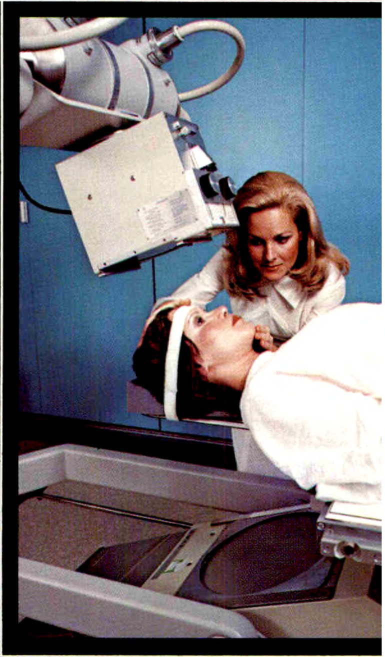

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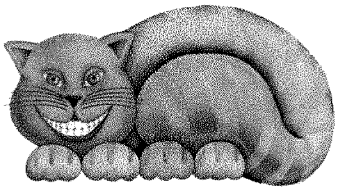

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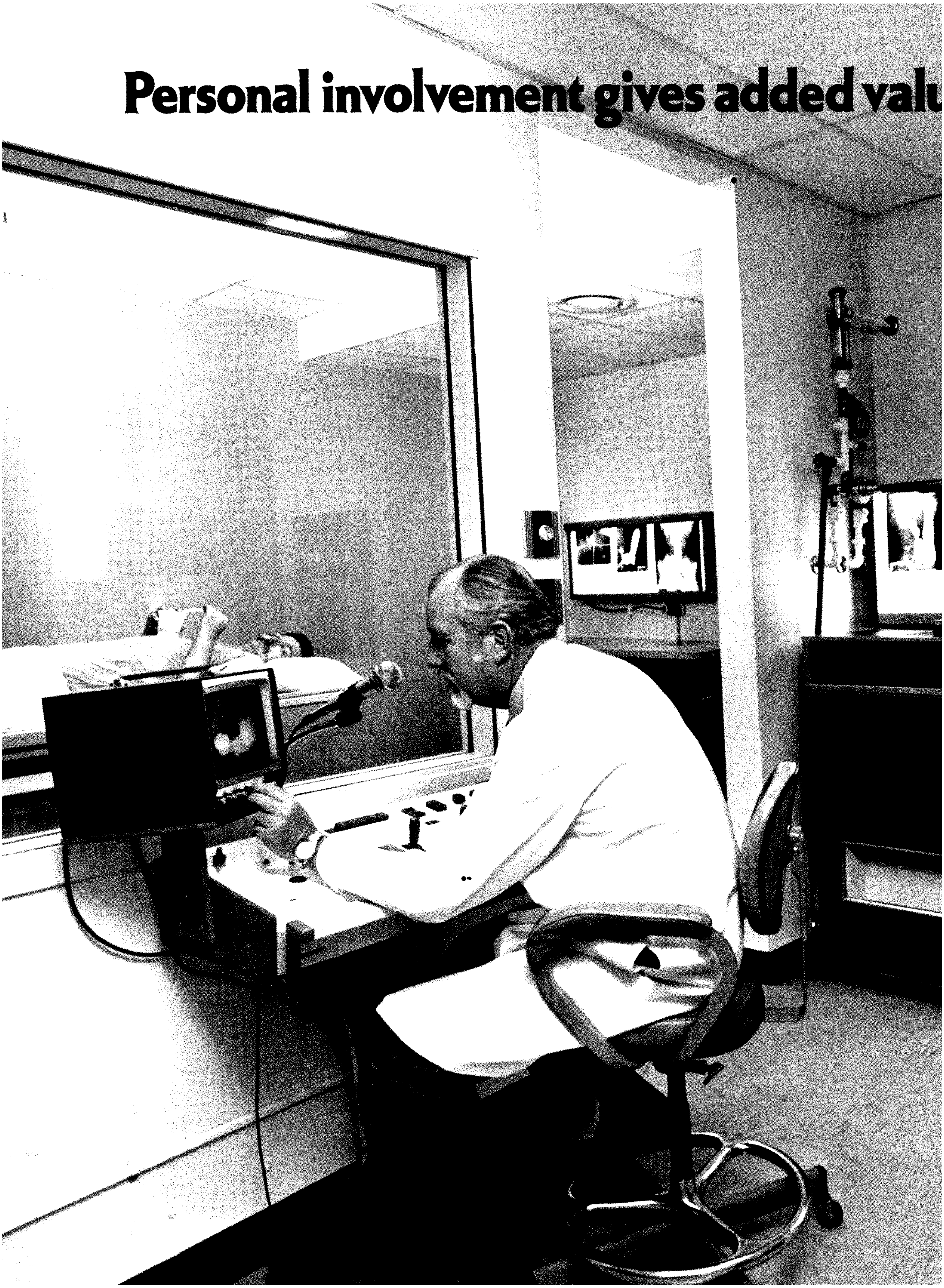

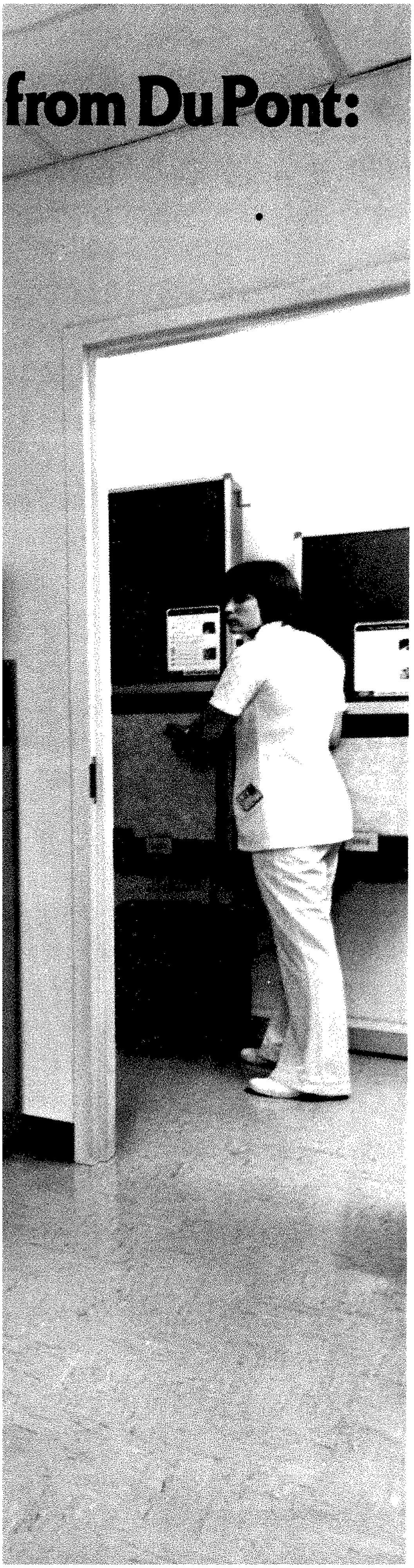

from Du Pont:

"The Daylight System helped reduce fluoroscopic exam time to 5 minutes per patient at Methodist Hospital of Indianapolis."

Gordon Ritchie (right), Du Pont Technical Representative, pictured with the Administrative Director of Radiology at Methodist Hospital.

Like many other hospitals, Methodist Hospital of Indianapolis, Inc., was experiencing a patient backlog in fluoroscopy exams. Times were in the 20-30 minute range.

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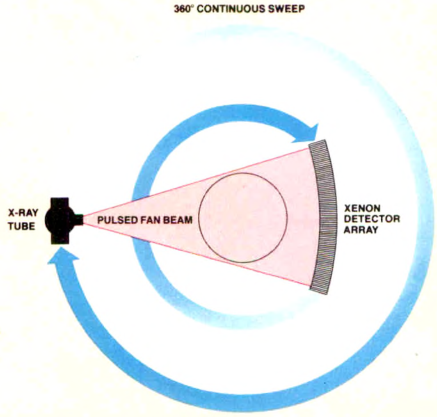
GE fast-scan computerized tomography: a whole new generation.



Third generation: GE's continuously rotating pulsed fan beam scanning. 5 to 10 seconds.

First and second generation units aren't fast enough for total body scanning.

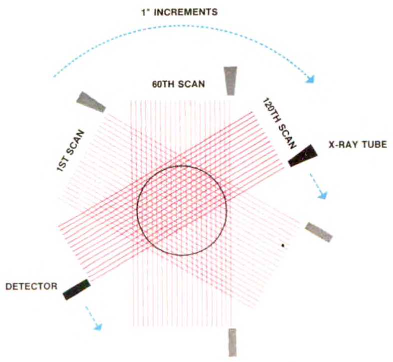
First and second generation computerized tomography systems have one major problem: image blurring caused by patient movement during body scans.

General Electric research has developed a fast-scan technology that is launching a new third generation of computerized tomography (CT) systems. The faster scans provide clear, sharp images.

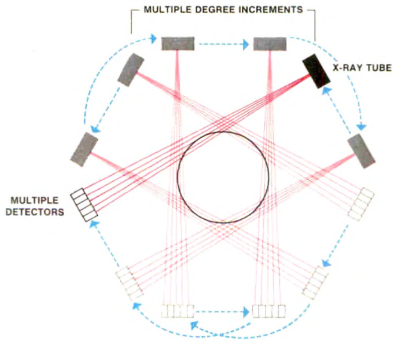
During body studies, patient movement caused by breathing can result in motion unsharpness. To really tackle this problem, a scan should take less time than a patient can hold his breath comfortably—10 seconds or less. However, existing computerized tomography systems cannot match this speed.

First generation units, using a pencil beam with a 1° incremental rotate-and-translate principle, take 4½ to 5½ minutes to complete a 180° scan.

Second generation systems use multiple pencil beams and more detectors—up to 30. Rotation is in larger angular increments. This configuration takes from 20 seconds to 3½ minutes per scan.



First generation: Pencil beam rectilinear scanning. 4½ to 5½ minutes.



Second generation: Multiple pencil beam rectilinear scanning. 20 seconds to 3½ minutes.

GE develops continuously rotating fan beam technology for fast-scan capability.

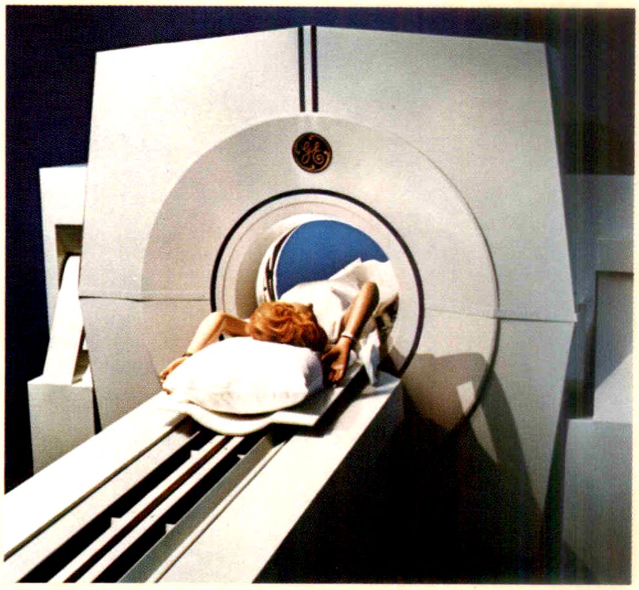
In developing an entirely new total body system, GE engineers and scientists abandoned the incremental rotate-and-translate approach of first and second generation units, with their inherent mechanical instability and resultant speed limitations. Instead, GE used a simpler, more stable mechanical approach, in which the tube and detectors rotate smoothly about the body in a continuous 360° scan, without need for translation.

This new third generation technology combines a continuously rotating, pulsed, wide fan x-ray beam with a unique high-pressure xenon detector array of up to 320 stable detectors. Advanced electronics are included to read out the huge volume of data. And GE has successfully conceived and implemented a new computational approach compatible with diverging fan beam geometry.

Third generation fast-scan technology proven on CT/M system.

GE's first application of fast-scan technology utilized computerized tomography's tissue density differentiation capability in the challenging area of breast examinations. This unit, called the CT/M system, is currently being clinically evaluated. Scans are completed in just 10 seconds. Patient handling is minimized. If you are interested in further information about the CT/M system, contact your GE representative or write for Publication 4675.

CT/M System


CT/T System

CT/T system performs body scans in less than 5 seconds.

The CT/T system for total body scanning is moving into the clinical environment. Scan time for the CT/T unit is 4.8 seconds. GE engineers believe this unprecedented scanning speed will provide consistently sharp, clear images for body studies. First production units are scheduled for the last half of 1976. The new CT/T systems represent the culmination of one of General Electric's most extensive research and development programs.

There's a corporate commitment behind GE scanning equipment.

All General Electric scanning systems are backed by the same company that has been serving radiology since the revolutionary Coolidge x-ray tube was introduced 63 years ago. And that kind of corporate dedication to excellence in medical equipment continues today . . . with the development of continuously rotating, pulsed fan beam technology.

As you consider CT scanning equipment, remember GE's continuous commitment to technology, product quality and service. That commitment is an important part of every GE medical system.

Fast-scan CT: backed by GE.

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General Electric continues its commitment to the total radiology department.

GE: innovation through technology.

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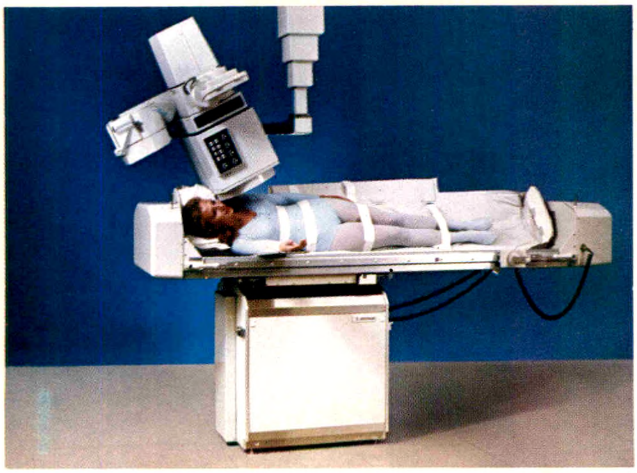
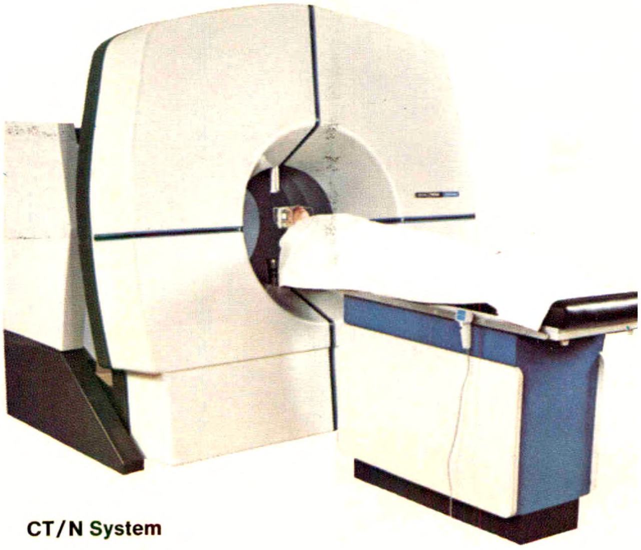


LAD System

When to use first and second generation CT scanners.

The slower scan times of first and second generation CT systems are acceptable for studies of the head. Here, the anatomy can be immobilized, reducing motion unsharpness.



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High quality image performance is provided at a moderate cost. For departments where economics and/or volume indicate a need for this type of scanner, GE offers the CT/N system . . . a dedicated neuro unit. Both first and second generation CT/N systems are available, with scan times of 4½ and 2 minutes, respectively. All CT/N systems feature Individual Patient Discs, which serve as a permanent patient record. These discs store up to eight tomographic scans which can be reconstructed and manipulated at the control console or a viewing unit at any time.

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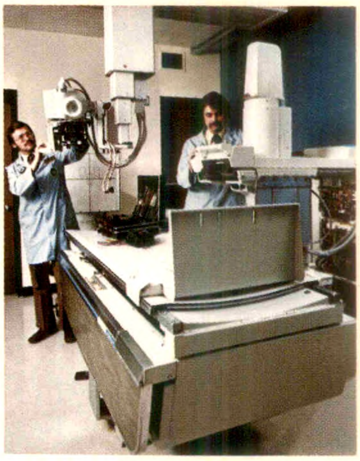

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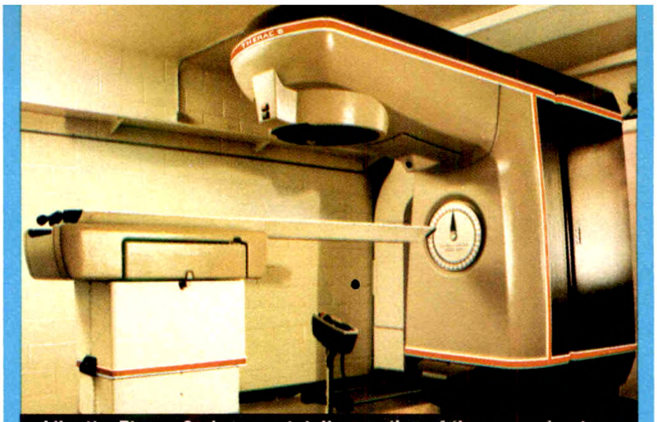

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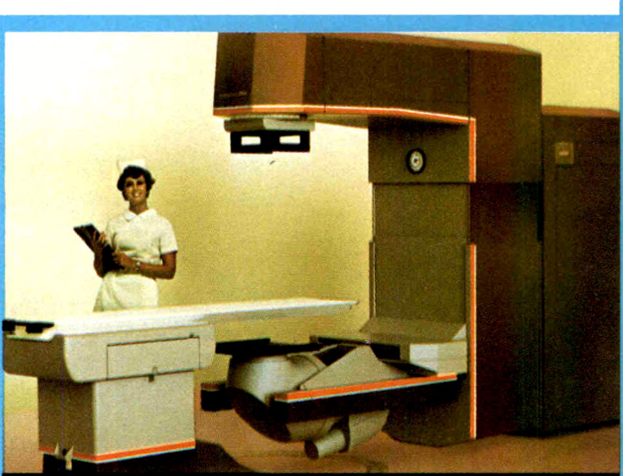

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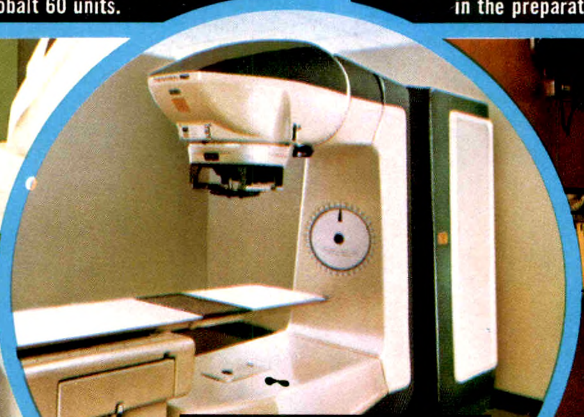

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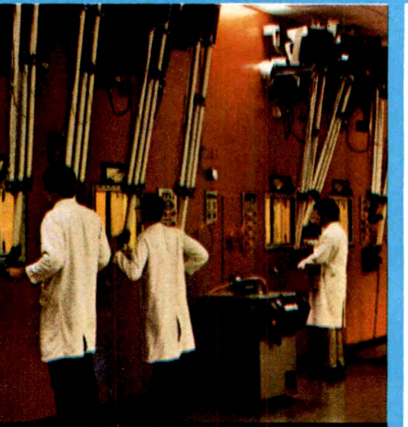

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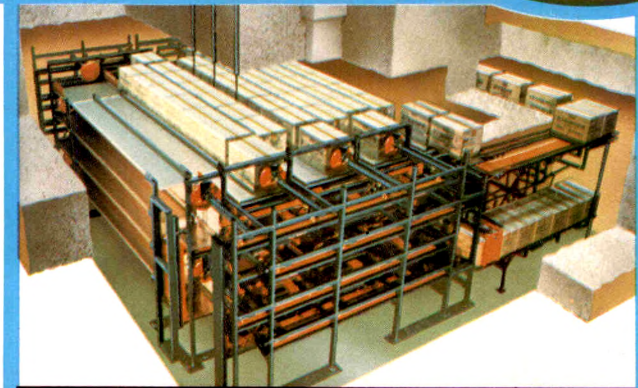

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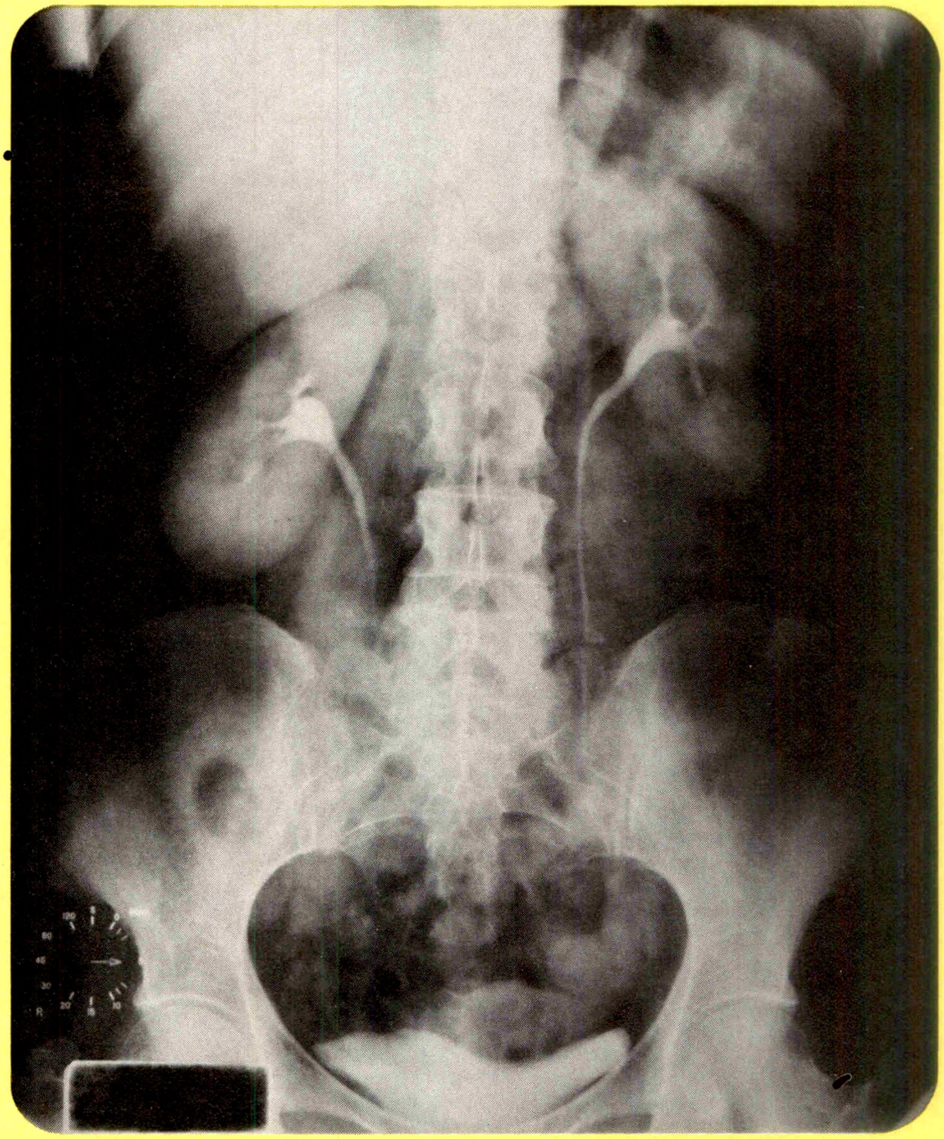

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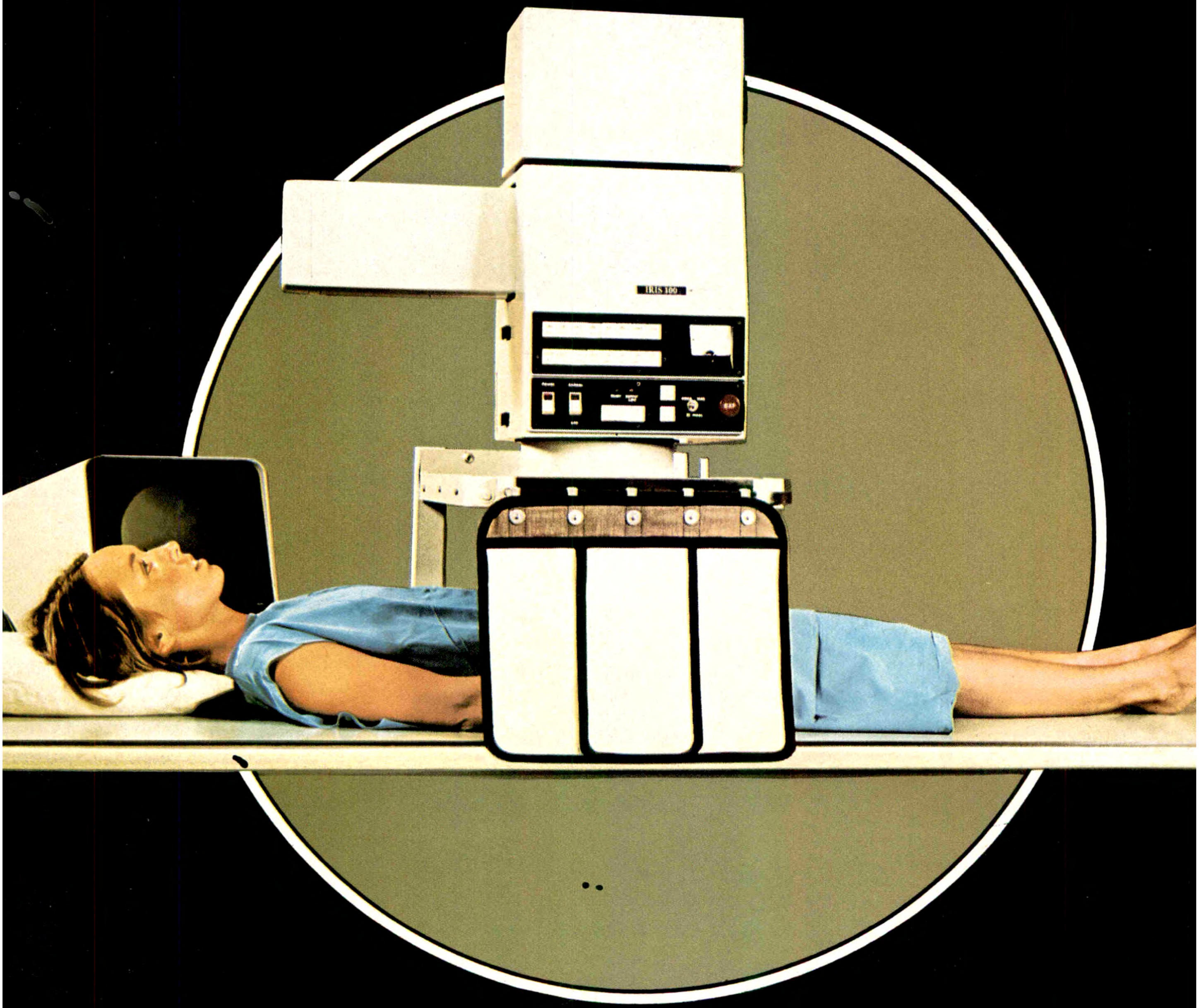

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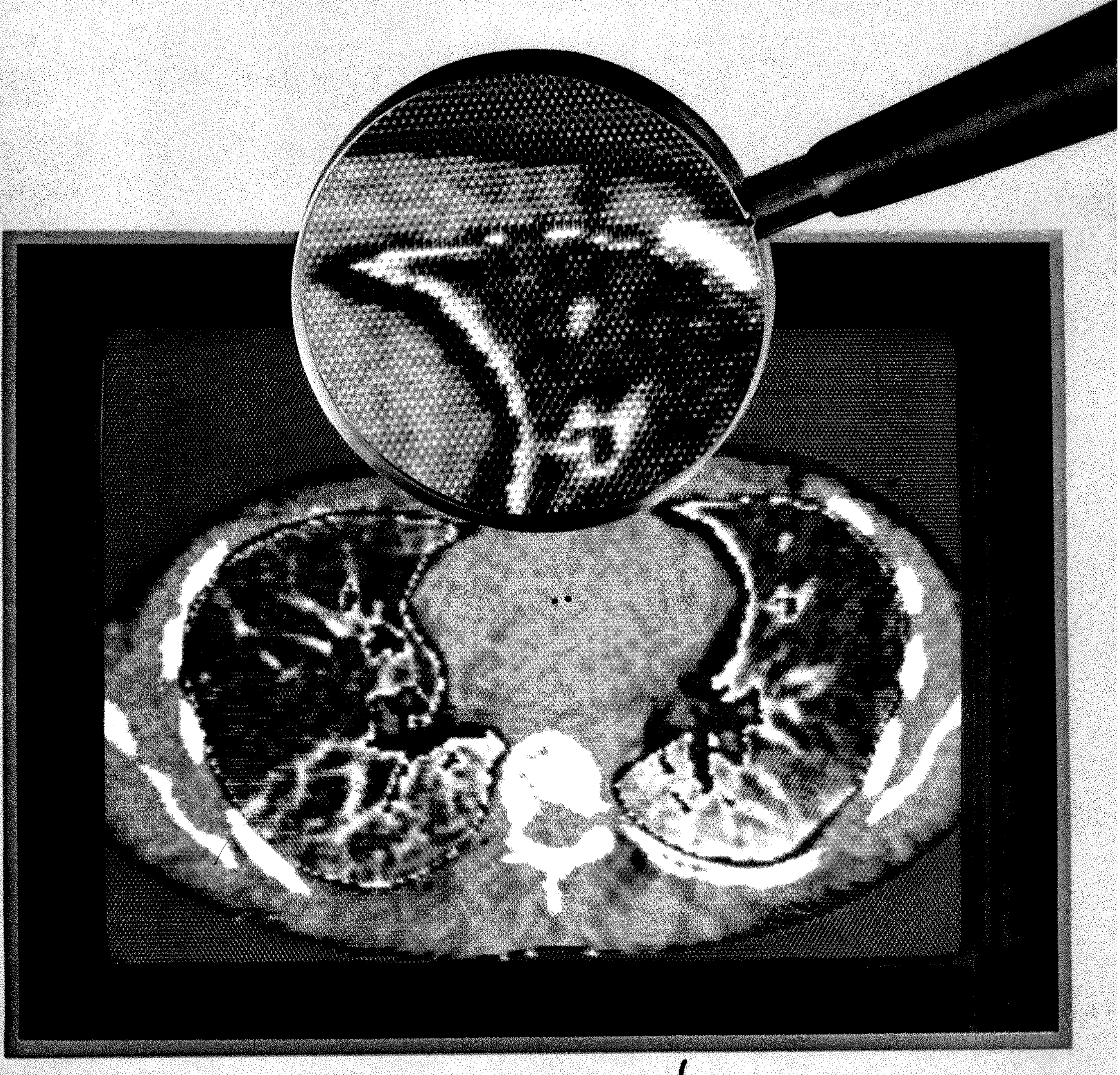

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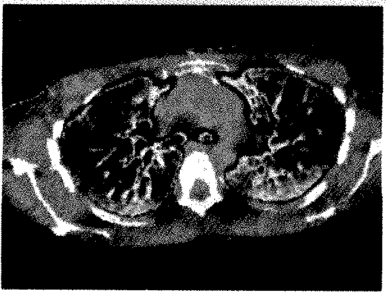

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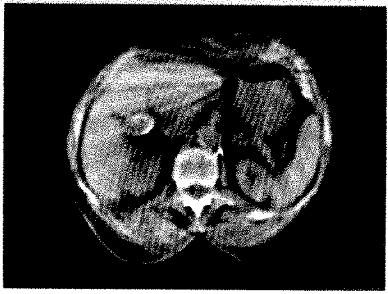

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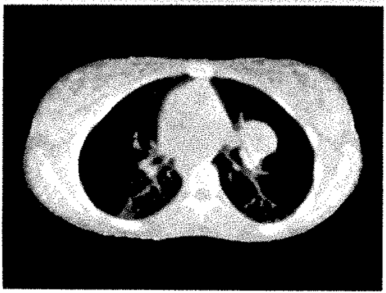

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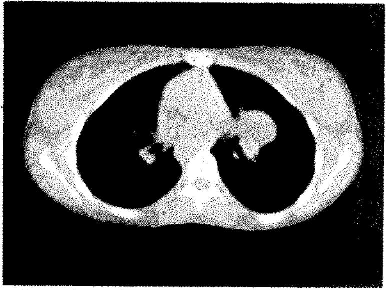

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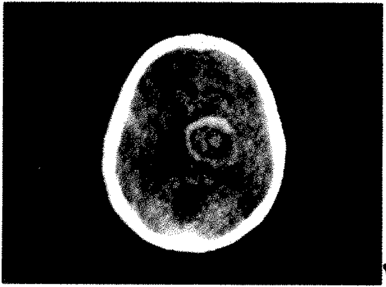

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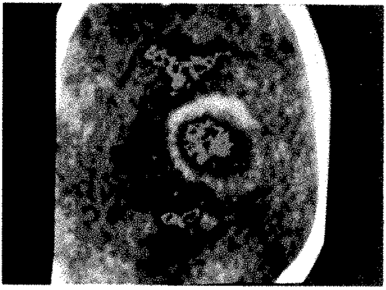

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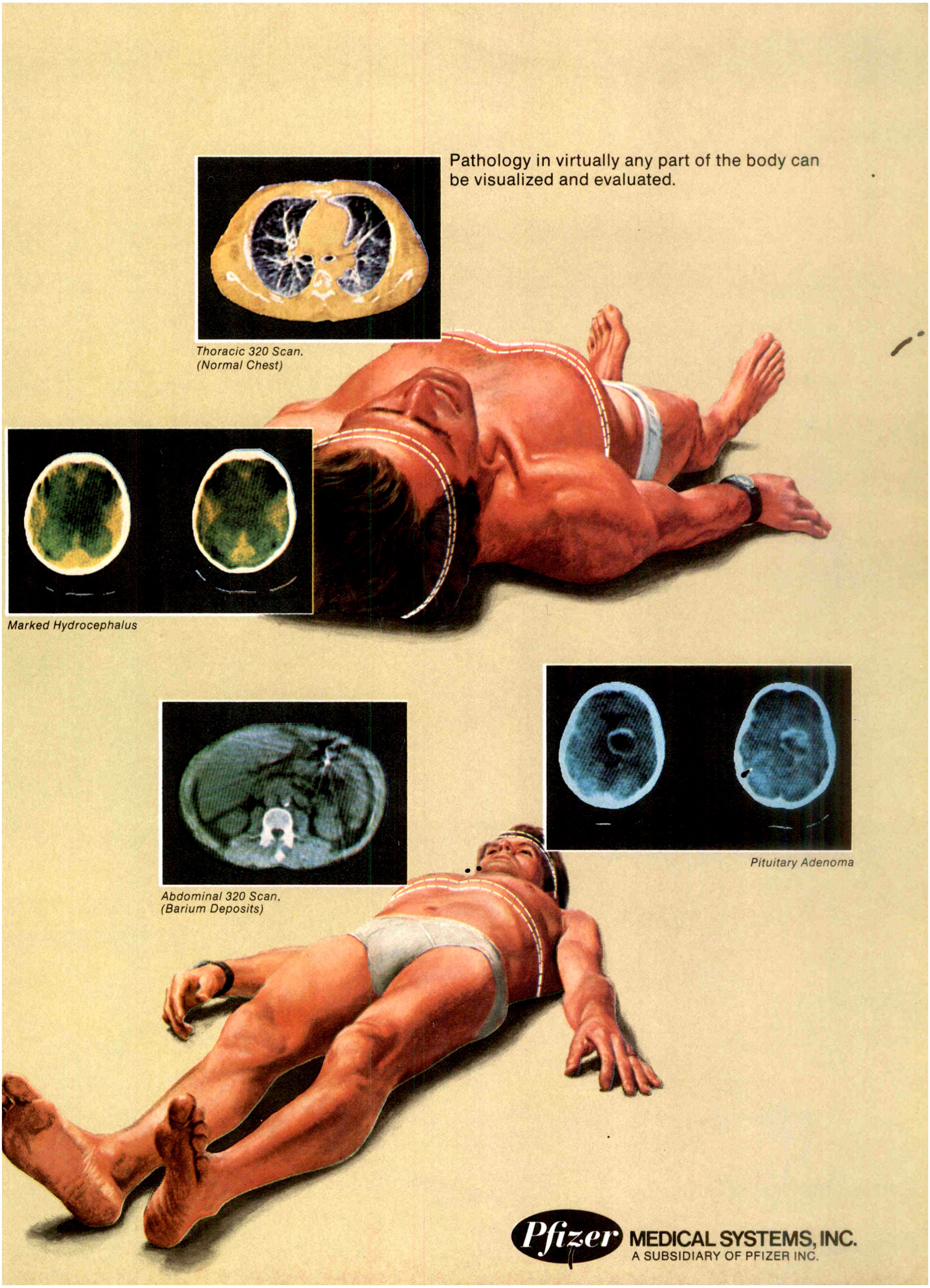

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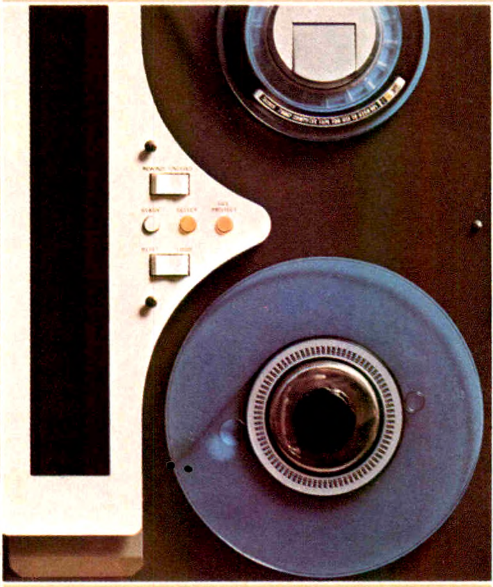

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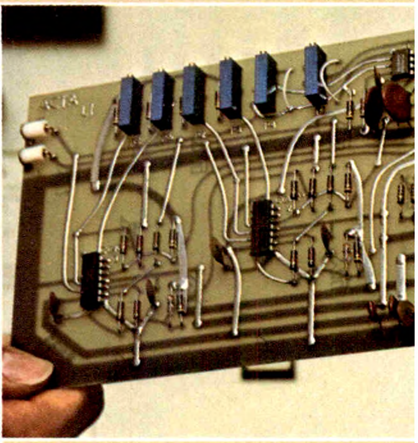

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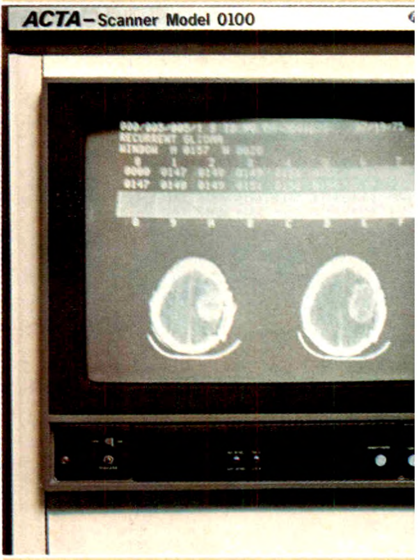

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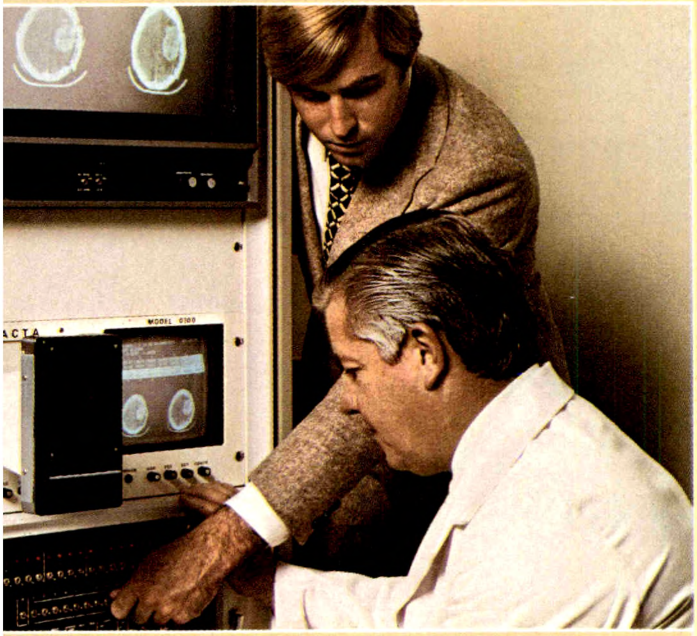

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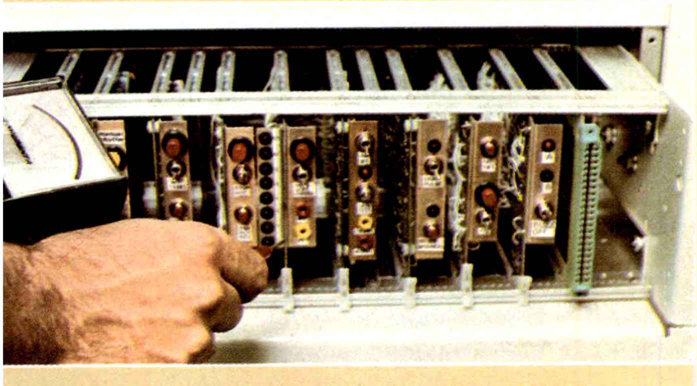

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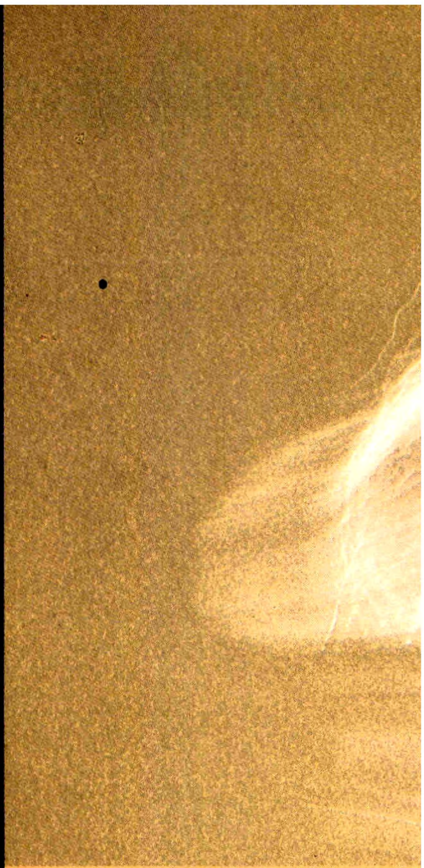

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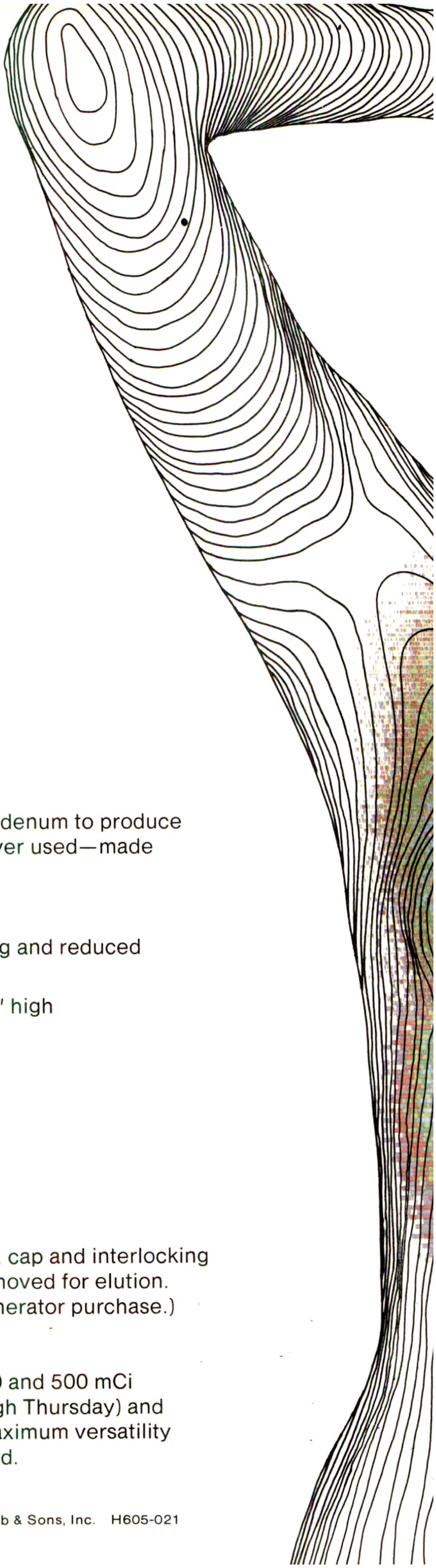

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Contraindications: At present, there are no known contraindications to the use of sodium pertechnetate ^{99m}Tc.

Warnings: Radiopharmaceuticals should be used only by physicians who are qualified by specific training in the safe use and safe handling of radionuclides, produced by nuclear reactor or cyclotron, and whose experience and training have been approved by the appropriate federal or state agency authorized to license the use of radionuclides.

This radiopharmaceutical should not be administered to women who are pregnant or who may become pregnant or during lactation unless the information to be obtained outweighs the possible potential risks from the radiation exposure involved. Ideally, examinations using radiopharmaceuticals, especially those elective in nature, of a woman of childbearing capability should be performed during the first few (approximately 10) days following the onset of menses.

Since radioactive pertechnetate is secreted in milk during lactation, formula-feedings should be substituted for breast-feedings.

Important: Since material obtained from the generator may be intended for intravenous administration, aseptic technique must be strictly observed in all handling. Only the eluent provided should be used to elute the generator. Do not administer material eluted from the generator if there is any evidence of foreign matter.

Precautions: As in the use of any other radioactive material, care should be taken to insure minimum radiation exposure to the patient consistent with proper patient management and to insure minimum radiation exposure to occupational workers.

At the time of administration, the solution should be crystal clear.

Adverse Reactions: At present, adverse reactions have not been reported following the use of sodium pertechnetate ^{99m}Tc.

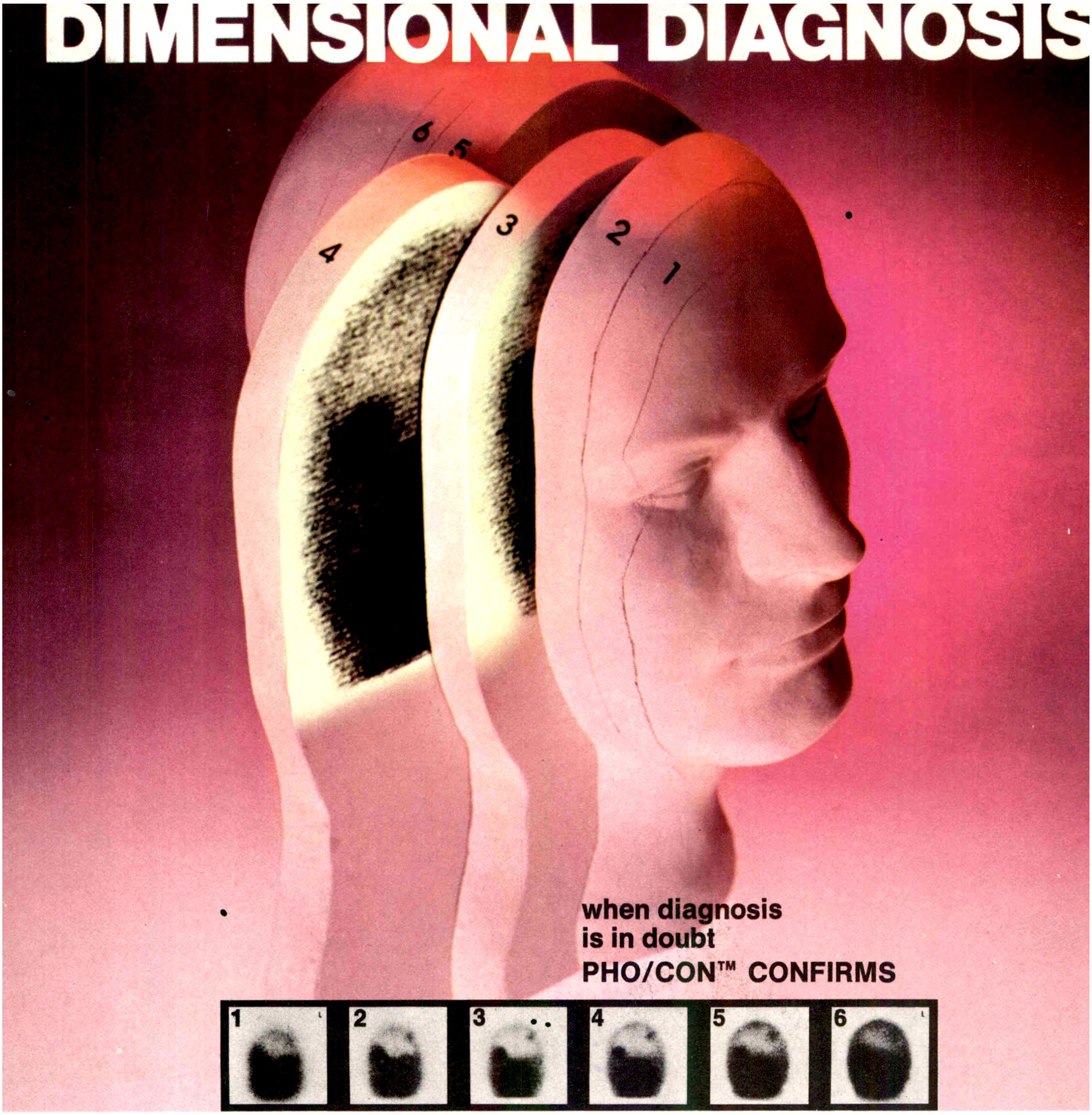
For complete prescribing information, consult package insert.

How Supplied: Minitec (Technetium 99m) Generator is available in potencies of 50, 100, 200, 300, 400, and 500 mCi. Supplied with the generator are vials of eluent containing 5 ml. of a sterile, non-pyrogenic solution of 0.9% sodium chloride in water for injection. Also supplied is suitable equipment for eluting, collecting, and assaying the technetium 99m.

Medotopes®

SQUIBB HOSPITAL DIVISION
E. R Squibb & Sons, Inc.
Princeton, N.J. 08540

DIMENSIONAL DIAGNOSIS



PHO/CON — the first of a new generation of multi-plane imaging devices — gives you significant new dimensions, whether you are imaging the brain, whole-body organs, individual organs, or bone. It can quickly confirm lesions masked by normal anatomical structures and provide definitive visualizations when other methods fail.

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PHO/CON utilizes two detector heads for simultaneous anterior-posterior imaging. It has a 26″ x 70″ scan field, suitable for any size study. Each detector head produces six simultaneous 2″ x 2″ tomographic images on 5″ x 7″ film, or three simultaneous 2″ x 5½″ whole body images on 8″ x 10″ film.

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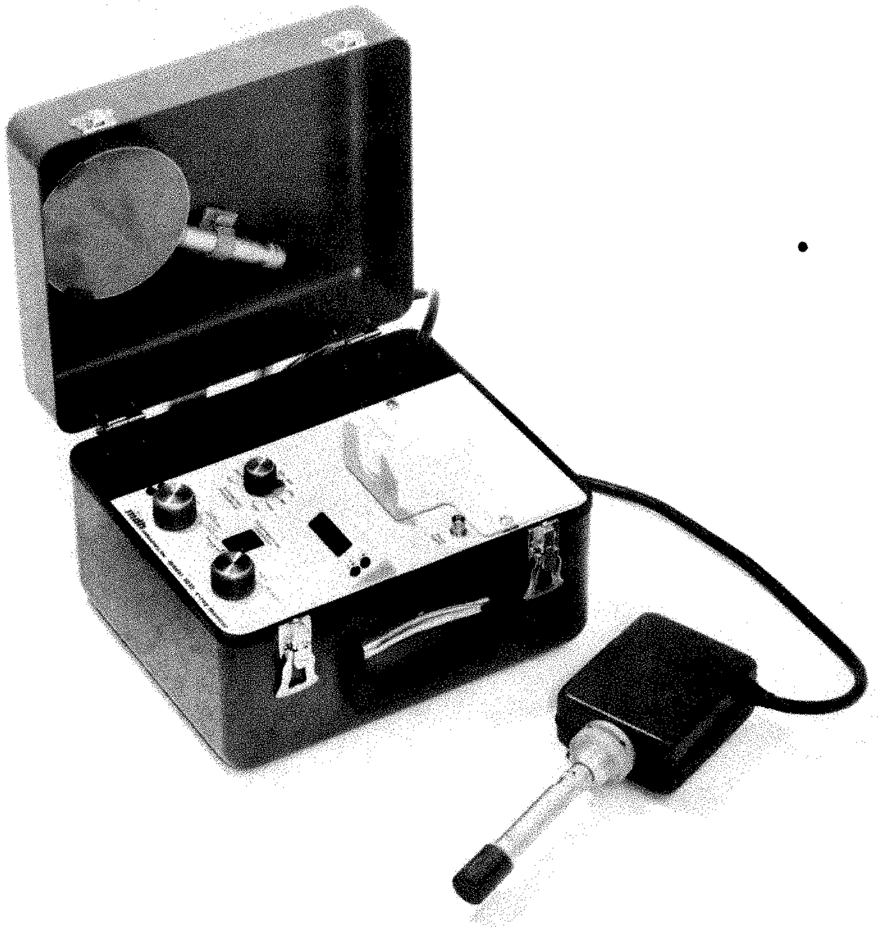

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Dr.__________________________

Remarks__________________________

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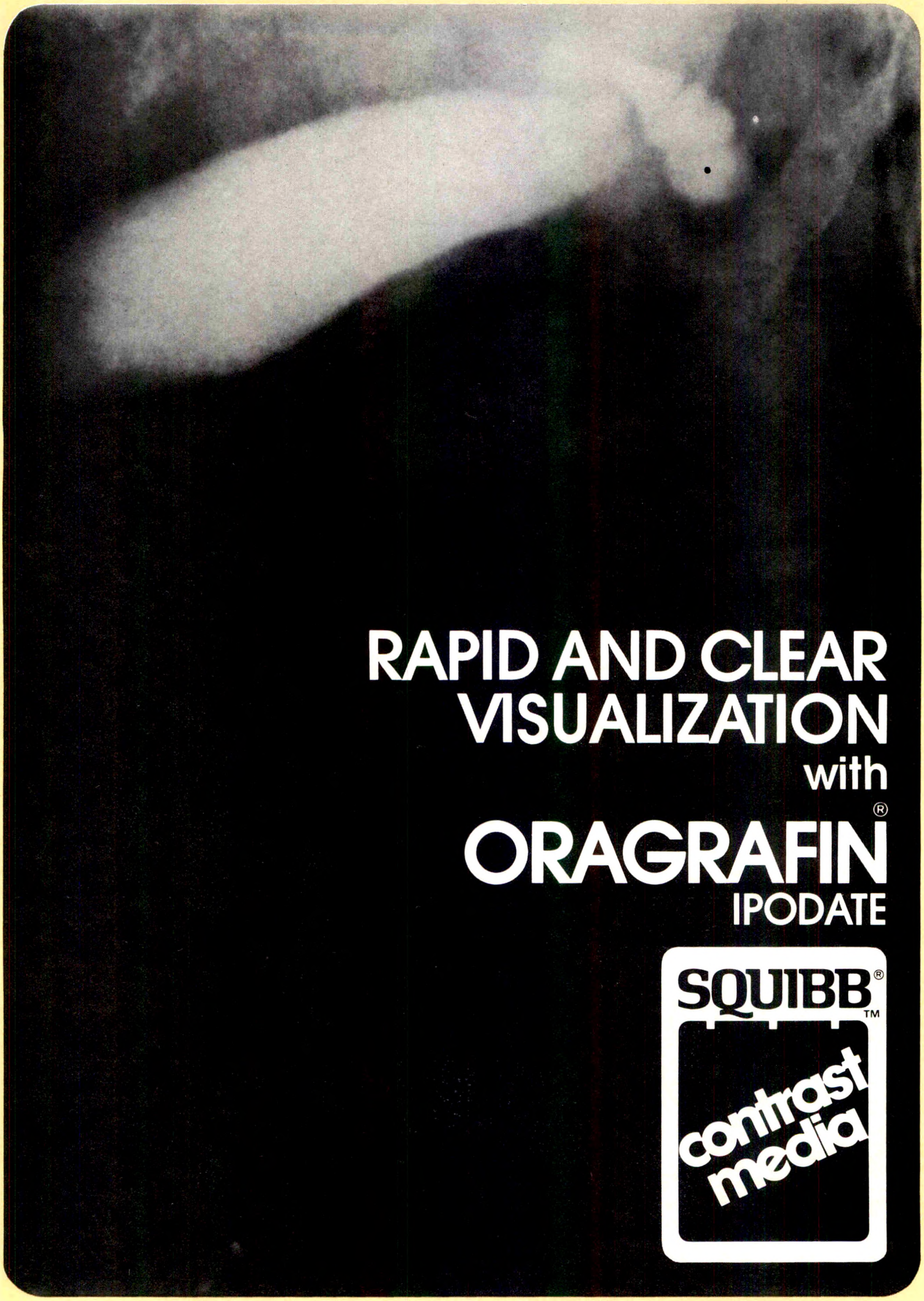
The
Reason
is
Clear...
Effectiveness


RAPID AND CLEAR VISUALIZATION
with
ORAGRAFIN®
IPODATE
SQUIBB®
™
contrast media

- Visualization of the ducts occurs in 1 to 3 hours and of the gallbladder within 5 hours or less with Oragrafin Calcium Granules (Calcium Ipodate for Oral Suspension N.F.).
- The gallbladder is opacified approximately 10 hours after ingestion of Oragrafin Sodium Capsules (Sodium Ipodate Capsules N.F.).
- Rapid absorption often permits visualization of even poorly functioning gallbladders. An unprepared patient can be studied the same day.
- When patients cannot take capsules, the granules are a convenient, palatable alternative.
- Both salts are usually well tolerated.

Dosage Schedules

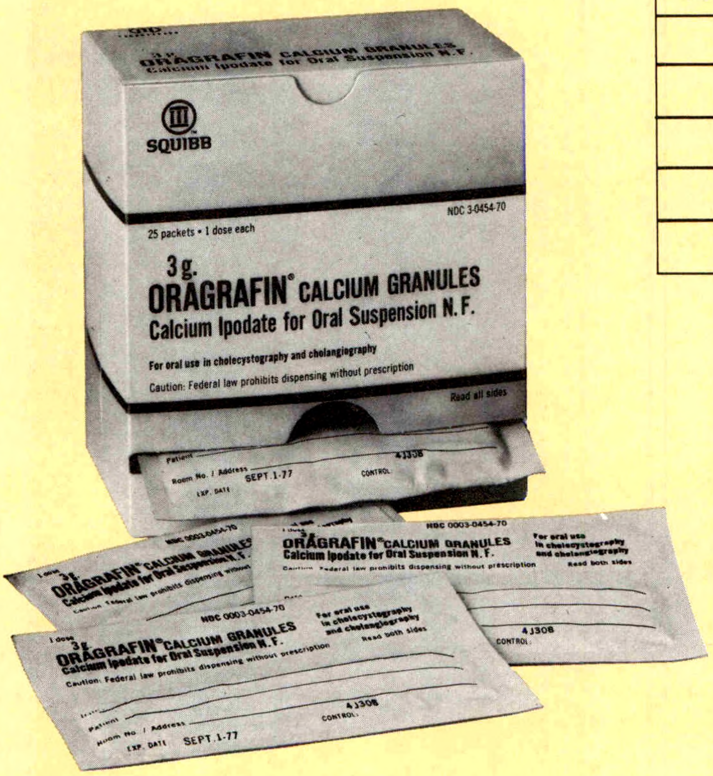
FOR ROUTINE OVERNIGHT PROCEDURES
Sodium Ipodate Capsules and/or Calcium Ipodate for Oral Suspension

	Gallbladder Films		Films of the Gallbladder and Biliary Ducts
11 P.M.	6 Capsules OR (or 12 Capsules)	1 packet of Granules (or 2 packets)	6 Capsules (or 1 packet of Granules, if preferred) and
next morning, 8 A.M.			1 packet of Granules
9 A.M.	Visualization of gallbladder	Visualization of gallbladder	Visualization of ducts and gallbladder
10 A.M.			
11 A.M.			

FOR RAPID, SAME-DAY PROCEDURES
Calcium Ipodate for Oral Suspension

	Films of Gallbladder and Ductal System
8 A.M.	2 packets of Granules
9 A.M.	Visualization of ducts
10 A.M.	Optimal visualization of ducts
1 P.M.	Visualization of gallbladder

See next page for complete prescribing information.


SQUIBB
25 packets • 1 dose each
NDC 3-0454-70
3 g.
ORAGRAFIN® CALCIUM GRANULES
Calcium Ipodate for Oral Suspension N.F.
For oral use in cholecystography and cholangiography
Caution: Federal law prohibits dispensing without prescription
Read all sides

ORAGRAFIN®
CALCIUM GRANULES
Calcium Ipodate for Oral Suspension N.F.

ORAGRAFIN®
SODIUM CAPSULES
Sodium Ipodate Capsules N.F.

the reason is clear

ORAGRAFIN®
CALCIUM GRANULES
Calcium Ipodate for Oral Suspension N.F.

ORAGRAFIN®
SODIUM CAPSULES
Sodium Ipodate Capsules N.F.

DESCRIPTION
Oragrafin Calcium Granules (Calcium Ipodate for Oral Suspension N.F.) and Oragrafin Sodium Capsules (Sodium Ipodate Capsules N.F.) are oral radiopaque media for cholangiography and cholecystography. *Calcium* ipodate is available in single-dose foil packets providing 3 g. calcium ipodate as granules dispersed in flavored sucrose. When mixed with water, the granules produce a pleasantly-flavored suspension. *Sodium* ipodate is available in capsules providing 500 mg. sodium ipodate per capsule.

The organically bound iodine content of calcium ipodate and sodium ipodate is 61.7% and 61.4%, respectively.

ACTIONS
Calcium ipodate and sodium ipodate are absorbed from the gastrointestinal tract, excreted by the liver into the bile, and stored and concentrated in the gallbladder. The calcium salt, which is absorbed somewhat faster than the sodium salt, appears in the ducts as early as 30 minutes after ingestion. Optimal concentration of either salt in the hepatic and biliary ducts occurs within 1 to 3 hours after ingestion in nearly all cases; rarely, maximal opacification may be delayed for as much as 5 hours. Adequate opacification of the ducts usually persists for about 45 minutes. The ducts may be visualized in patients who have undergone cholecystectomy.

The gallbladder is optimally opacified approximately 10 hours after ingestion of either salt. Diagnostically adequate filling, however, often takes place within 5 hours or less after ingestion, particularly with the calcium salt. Thus, studies of ducts and gallbladder may be carried out in as little as 5 hours when necessary or desirable. In this connection, it should be pointed out that both salts have been administered to unprepared patients as well as to previously prepared patients, with no significant difference in results.

INDICATIONS
Calcium ipodate and sodium ipodate are indicated for cholecystography. They may also be used for cholangiography, although they are not considered the drugs of choice.

CONTRAINDICATIONS
Both preparations are contraindicated in persons who are hypersensitive to ipodate salts.

WARNINGS
A history of sensitivity to iodine *per se* or to other iodinated compounds is not an absolute contraindication to the use of these preparations, but calls for extreme caution in administration.

Usage in Pregnancy
The safety of these preparations for use during pregnancy has not been established; therefore, they should be used in pregnant patients only when, in the judgment of the physician, their use is deemed essential to the welfare of the patient.

PRECAUTIONS
Increasing the dosage above that recommended increases the possibility of hypotension.

Anuria may result when these preparations are administered to patients with combined renal and hepatic disease or severe renal impairment.

Renal toxicity has been reported in a few patients with liver dysfunction who were given oral cholecystographic agents followed by urographic agents. Administration of urographic agents should therefore be postponed in any patient with a known or suspected hepatic or biliary disorder who has recently taken a cholecystographic contrast agent.

Gastrointestinal disorders which interfere with absorption and liver disorders which interfere with excretion may result in non-visualization of the hepatic and biliary ducts and the gallbladder.

Contrast agents may interfere with some chemical determinations made on urine specimens; therefore, urine should be collected before administration of the contrast media or two or more days afterwards.

Thyroid function tests, if indicated, should be performed prior to the administration of these preparations since iodine containing contrast agents may alter the results of these tests.

ADVERSE REACTIONS
Sodium ipodate and calcium ipodate are usually well tolerated. Unwanted effects such as mild and transient nausea, vomiting, or diarrhea sometimes occur but the incidence can be reduced by restricting the dosage to 3 g. and administering only the Granules to patients who may be prone to gastrointestinal reactions. Headache, dysuria, or abdominal pains may occur infrequently as transient disturbances.

Hypersensitivity reactions may include urticaria, serum sickness-like reactions (fever, rash, arthralgia), other skin rashes, and, rarely, anaphylactoid shock. They are more likely to occur in individuals with a history of allergy, asthma, hay fever, or urticaria, and in those who have previously demonstrated hypersensitivity to iodine compounds.

DOSAGE AND ADMINISTRATION
The Capsules should be taken with as little water as possible. They may be swallowed in rapid succession or slowly over the course of ½ hour or more, depending on patient preference.

The Granules should be stirred vigorously into a small amount of water (¼ glass or less) and swallowed immediately. If lukewarm rather than cold water is used, the patient will find the suspension quite palatable and there will be less likelihood of nausea.

A total dose of 6 g. (12 Capsules or 2 packets of Granules) per 24 hour period should not be exceeded.

When an upper gastrointestinal barium study is scheduled, prior administration of either salt will not interfere. Either salt may also be used in conjunction with an intravenous cholangiographic agent.

The recommended dosage and patient preparation for cholangiography and/or cholecystography are as follows:

Routine Cholecystography
On the day before the examination, the patient may, if feasible, eat a high-fat lunch so that the gallbladder will evacuate and refill with opacified bile. The evening meal, which should be light and fat-free, should be eaten 2 hours before the contrast medium is taken. The contrast agent should be administered 10 to 12 hours before the roentgenologic examination. The usual dose is 6 Capsules (providing 3 g. sodium ipodate), although up to 12 Capsules may be given; 1 to 2 packets of Granules may be used instead. No other food or drink except small amounts of water should be taken before the examination. A mild laxative or other cathartic may be given, but is not generally necessary.

Roentgenologic examination of the gallbladder is performed the next morning in the usual manner, employing the standard positions. An immediate study of the wet films will determine any need for repositioning of the patient. Administration of a fat meal or other cholecystokinetic agent provides good dynamic studies of gallbladder function. If a barium meal examination is also to be performed, the fat meal may be given simultaneously with or following the barium meal. Gallbladder function studies are then made after the barium meal examination is completed.

Cholangiography
No prior preparation of the patient is necessary. For this procedure, the Granules should be used. They are administered one hour before cholangiography. Although only one packet (providing 3 g. calcium ipodate) may suffice, two packets (6 g.) are usually necessary for visualization of the ducts.

Beginning one hour after ingestion of the Granules, and at 15-minute intervals thereafter, films should be taken, preferably with the aid of tomography or laminography. With proper positioning of the patient, residual contrast medium in the gastrointestinal tract is not likely to be a problem, particularly with the more rapidly absorbed calcium salt. Optimal visualization of the ducts is generally achieved between 1½ and 2½ hours after ingestion of the medium.

Combined Cholangiography and Cholecystography
Preparation of the patient and administration of dosage should be as outlined under *Routine Cholecystography*, with a dosage of 6 Capsules or, if preferred, one packet of Granules taken on the evening before examination. On the following morning, one hour before the examination, one additional packet of Granules should be administered.

Beginning one hour after the morning dose, and at 15-minute intervals thereafter, films should be made, preferably with the use of tomography or laminography. While the gallbladder will have concentrated the evening dose of the medium, the additional morning dose will provide opacification of the ducts, and simultaneous visualization may be achieved. When satisfactory films have been obtained, a fat meal may be administered to provide gallbladder function studies.

Rapid Combined Cholangiography and Cholecystography
No prior preparation of the patient is necessary. On the day of examination, the patient should be given two packets of Granules. Beginning one hour later, examination of the ducts should be performed as described under *Cholangiography*. If the gallbladder has not opacified sufficiently by the time the cholangiographic examination is completed, further cholecystograms may be taken after 2 or 3 hours. Dynamic studies of gallbladder function may be carried out in the usual manner.

HOW SUPPLIED
Oragrafin Calcium Granules (Calcium Ipodate for Oral Suspension N.F.), single-dose foil packets; boxes of 25 packets (3 g. calcium ipodate per packet). Oragrafin Sodium Capsules (Sodium Ipodate Capsules N.F.), boxes of 25 vials (6 capsules each vial); bottles of 100; and Unimatic® single-dose packages of 100.

SQUIBB HOSPITAL DIVISION
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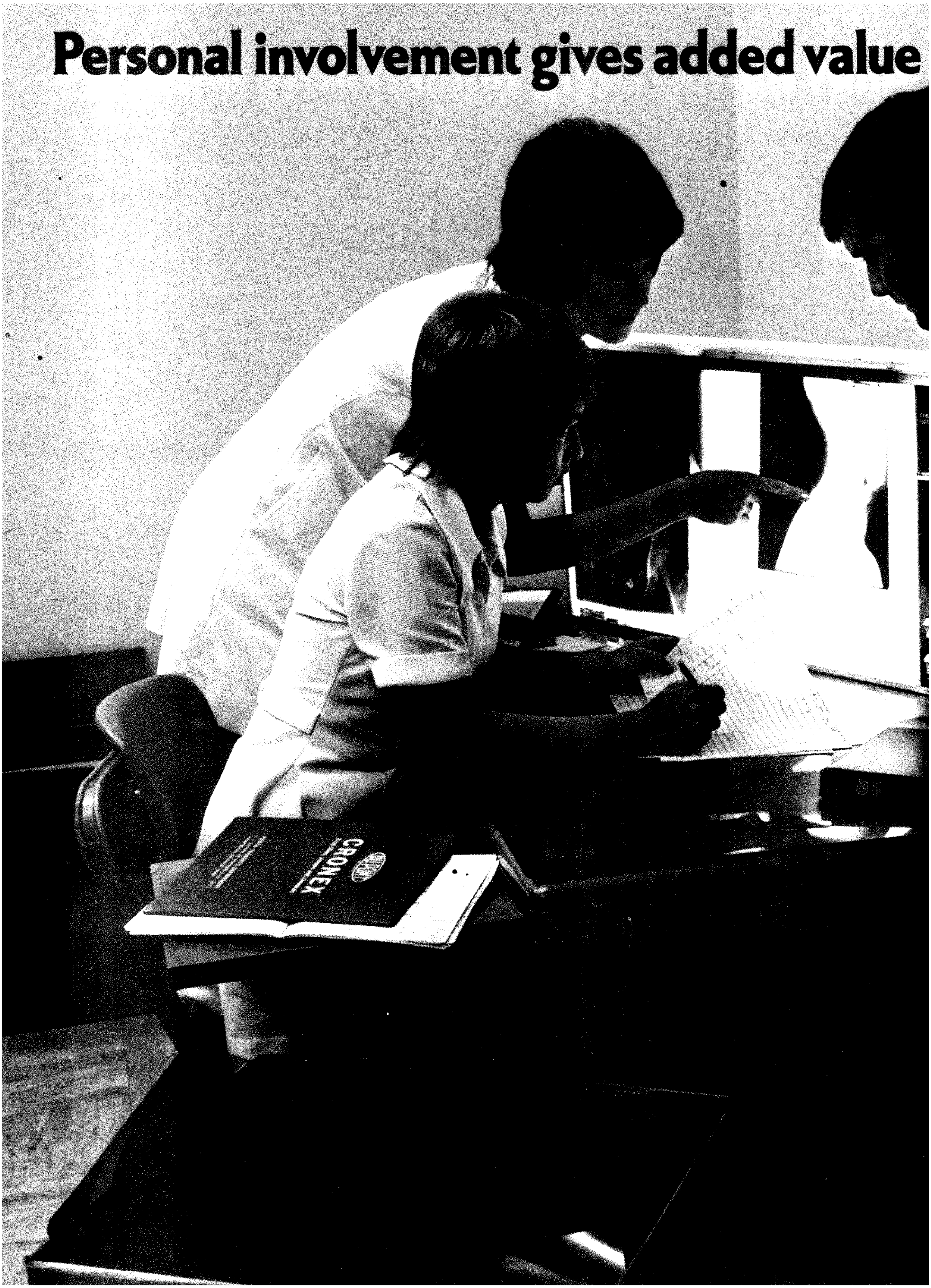
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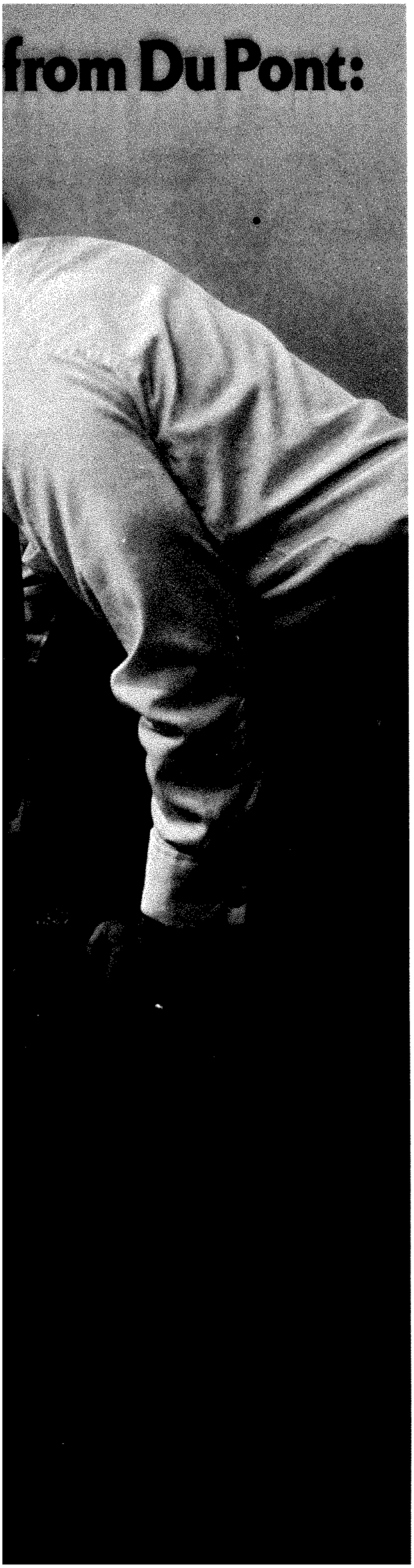
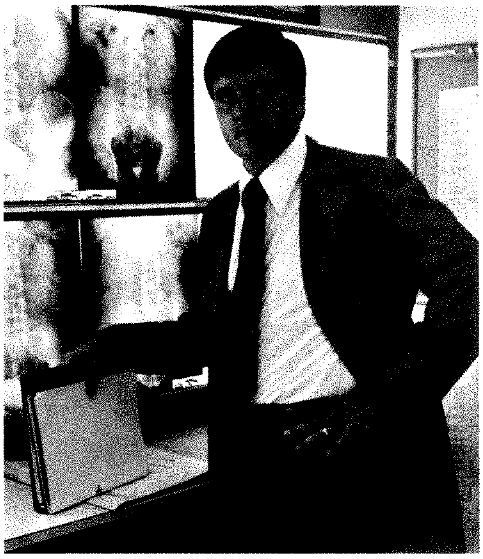


"We cut the X-ray retake rate by 50% and reduced annual film cost by almost 10% at St. Vincent's Medical Center in Jacksonville."



Hank Ward,
Du Pont Sr. Technical
Representative.

Ms. Rae Walker, R.T., Administrative Supervisor at St. Vincent's in Jacksonville was pleased with the X-ray Department's low retake rate until Hank Ward showed her how Du Pont, with the help of Department personnel, could cut an additional 50% off the rate, and almost 10% off her annual film budget.

Working with Rae and her Chief Technologist, Judy Walsh, Hank developed a program that identified variables causing retakes. After an analysis of these variables, the team established corrective procedures, and most of the variables were eliminated.

The result: a reduction in retakes by half, a significant cost saving, and more consistent radiographic quality. In Rae's own words, she didn't believe it could be done, but Du Pont delivered as promised.

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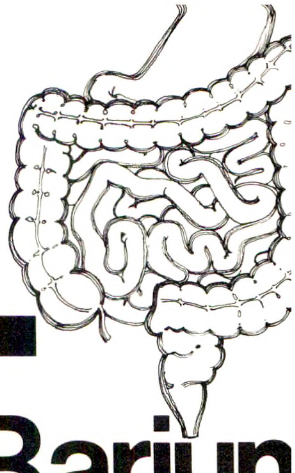

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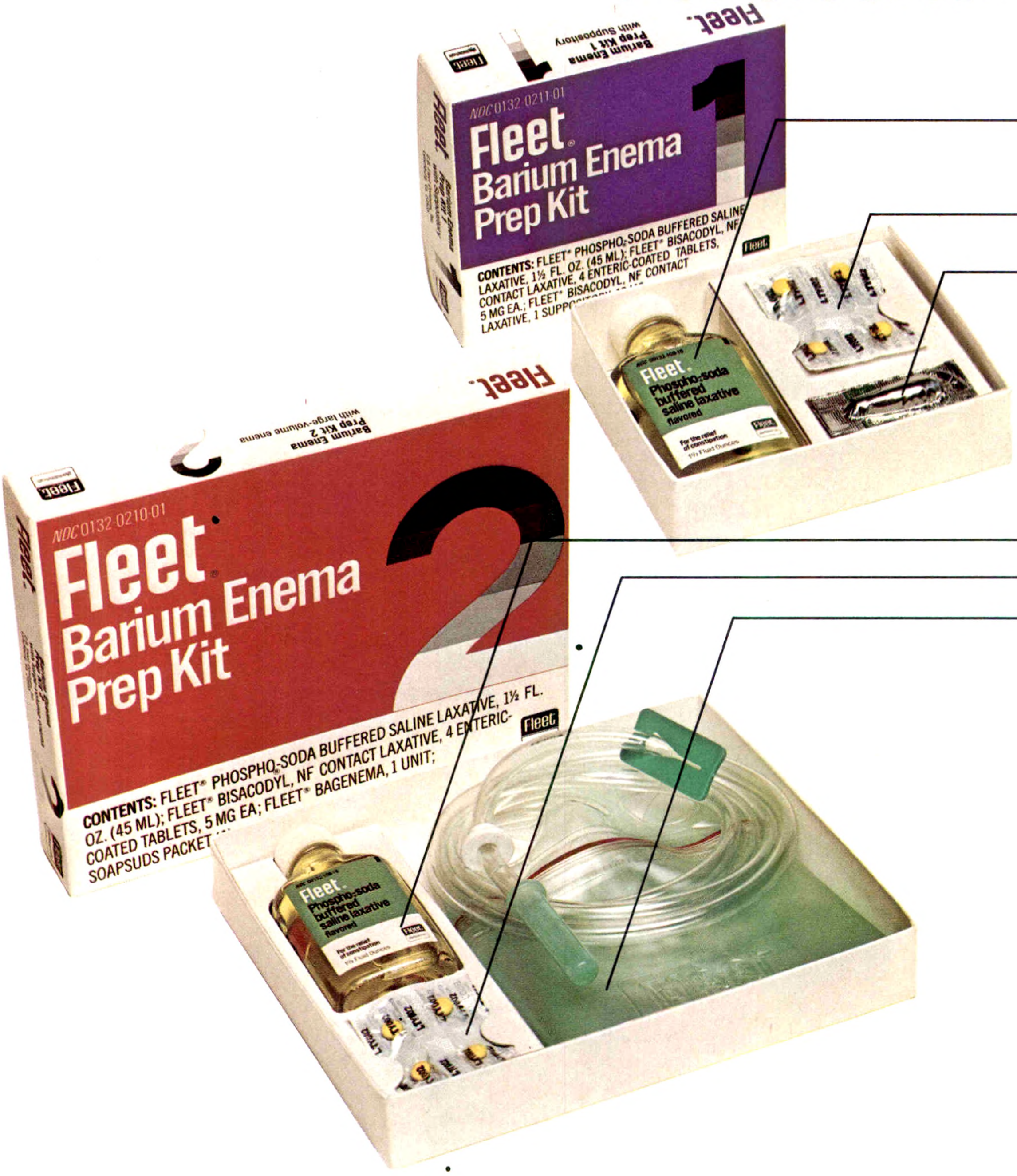
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with Suppository
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Prep Kit
1
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Fleet
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saline laxative
flavored
For the relief of constipation
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Fleet

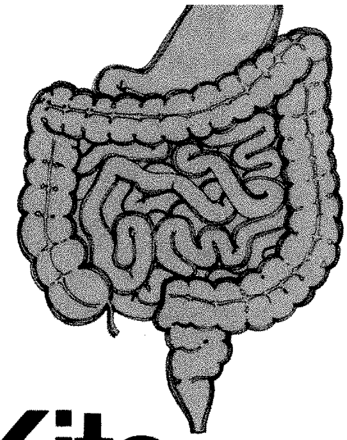
Fleet® Barium Enem Prep Kit No. 1 conta

1½ oz of **Fleet Phospho®-Soda,** buffered saline laxa to stimulate the sma intestine;
four **Fleet® Bisacod Tablets,** contact lax for colon stimulatio
one **Fleet® Bisacod Suppository,** contac laxative for final evacuation prior to examination.

Fleet® Barium Enem Prep Kit No. 2 conta

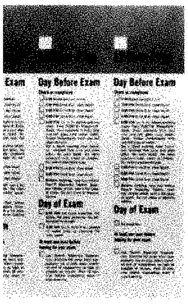
1½ oz of **Fleet® Phospho®-Soda;**
four **Fleet® Bisacod Tablets;**
one **Fleet® Bagenen** a large-volume disp able enema for final evacuation prior to examination.

or not



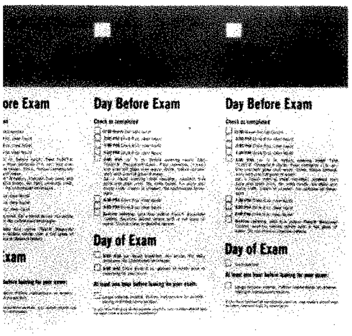
nema Prep Kits

learer x-rays, and fewer retakes



Exam Day Before Exam Day Before Exam

Day of Exam Day of Exam



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The all-new Fleet Barium Enema Prep Kits are complete prepping systems that assure thorough and reliable colon cleansing prior to a barium enema exam.

☐ **With effective and balanced methods of prepping**
Utilizing a combination of diet, hydration, and evacuation, the Fleet Barium Enema Prep Kits meet all the criteria for preparing the colon for examination as recommended by the American College of Radiology Ad Hoc Committee on Detection of Cancer of the Colon.[1]

☐ **Available in two convenient forms**
There are two Fleet Barium Enema Prep Kits, so that now you have the option of choosing the final step that you prefer—enema or suppository.

☐ **With easy-to-follow instructions**
Each Fleet Barium Enema Prep Kit supplies clearly written, concise instruction sheets for easy, dependable administration by the nurses in the ward or by your patient at home. Check-off boxes ensure completion of each step.

☐ **With a flexible time-table**
The Fleet Barium Enema Prep Kits also offer three convenient time schedules —12, 18, or 24 hours. So now, you can tailor the prepping to fit better into your schedule and your patient's routine.

"In my experience across the country, talking to technicians and doctors, ... the greatest defect in colon examinations, ... is in the preparation of the colon."[2]

For better colon preparation and fewer repeat examinations, use Fleet Barium Enema Prep Kits routinely —as your prepping agent of choice in the Radiology Department and on an outpatient basis.

References:
1. *Detection of Colon Lesions,* First Standardization Conference, Amer. College of Radiology, (Chicago, Ill., 1973), pp. 203-204.
2. *Ibid,* p. 76.

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Macrotec®
Aggregated Albumin (Human)
for labeling with technetium 99m

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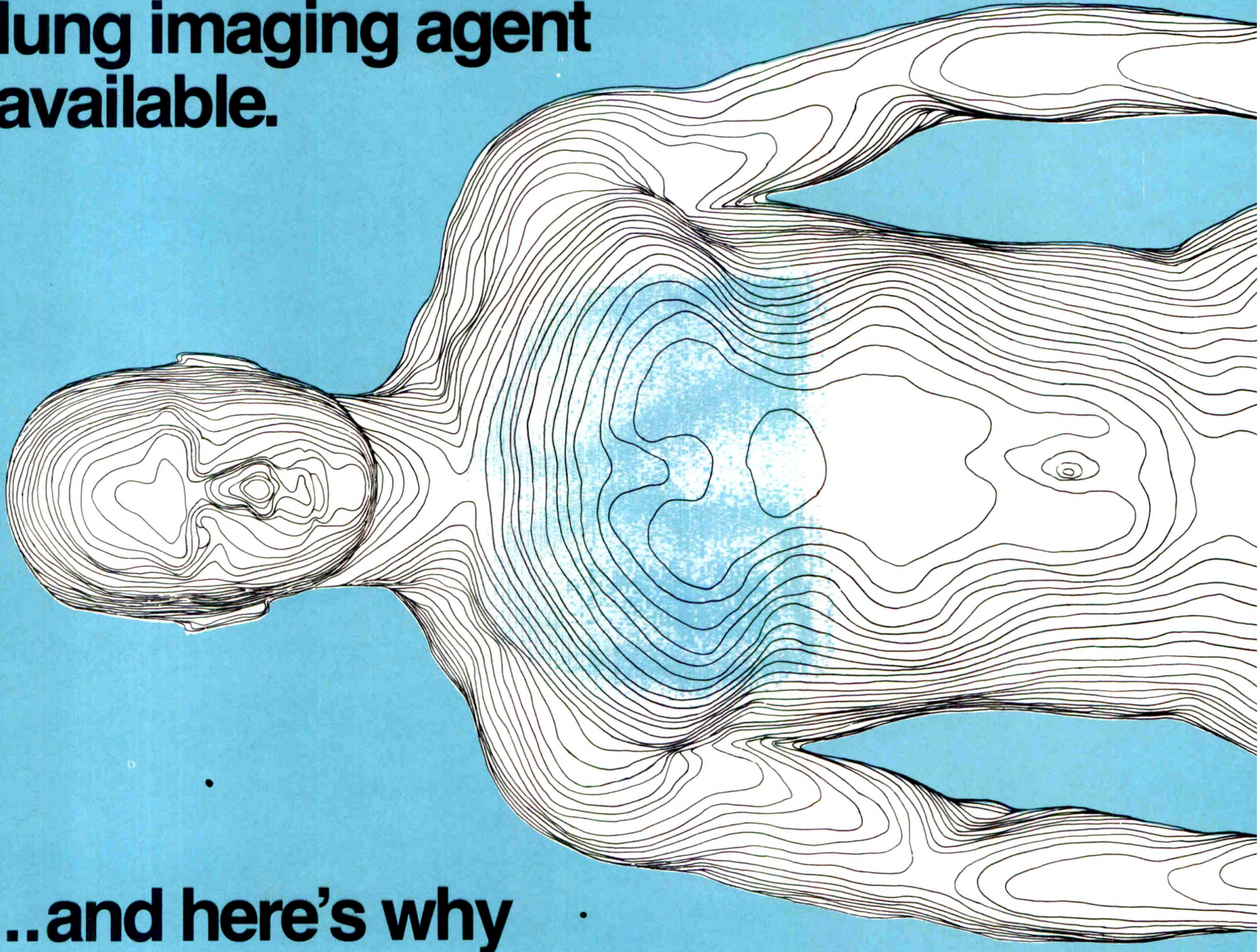

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Simple, two-step procedure. Not an ampul, not a frozen material. No waiting, no complicated procedures or specialized equipment required. Just two easy steps and you're ready to assay and inject.

Uniform particle size, excellent labeling efficiency. Particle size meets or exceeds Bureau of Biologics standards; 90% in 5-60 micron range. Excellent labeling efficiency when reconstituted with a compatible technetium 99m.

Won't agglomerate in the vial, loses virtually no labeling for 8 hours (if stored between 2°C. and 8°C.).

Ideal for the busy lab. Recommended amount of 99mTc for reconstitution high enough to allow numerous scans from a single vial.

BASIC STEPS IN PREPARING FOUR TECHNETIU

Squibb Macrotec® Aggregated Albumin (Human)	**1. Add 1-3 ml. of 99mTc.** Maintain shielding at all times.**	**2. Shake vigorously for 10-15 seconds.**
Mallinckrodt TechneScan™ MAA Aggregated Albumin (Human)	1. Remove reaction vial from *freezer* and *wait approximately 5 minutes* for contents to come to room temperature.	2. Add 99mTc.** Maintain shielding at all times.
3M Albumin Microspheres (Human)	1. Add 4-10 ml. of 99mTc.**	2. Shield completely and vigorously shake for 5-15 seconds.
Medi+Physics Lungaggregate™ Reagent Aggregated Albumin (Human)	1. Shake *ampul* vigorously to suspend particles.	2. Open ampul.

Emphasis added by Squibb to point out certain differences in procedures.

ACROTEC® (Aggregated Albumin [Human])

crotec (Aggregated Albumin [Human]) is a sterile, non-pyrogenic, lyophilized paration of aggregated albumin. Each vial of the preparation contains 0.08 mg. as chloride, 1.5 mg. denatured human serum albumin, and 10 mg. Normal um Albumin (Human).

DICATIONS: For use in perfusion lung imaging as an adjunct to other diagnos- procedures.

NTRAINDICATIONS: At present there are no known contraindications to the of this product.

RNINGS: Radiopharmaceuticals should not be administered to patients who pregnant, or during lactation, unless the benefits to be gained outweigh the ential hazards.

Ideally, examinations using radiopharmaceuticals, especially those elective in nature, of a woman of childbearing capability, should be performed during the first few (approximately 10) days following the onset of menses.

Since ^{99m}Tc is excreted in milk during lactation, formula-feedings should be substituted for breast-feedings.

Radiopharmaceuticals should be used only by physicians who are qualified by specific training in the safe use and handling of radionuclides produced by nuclear reactor or particle accelerator and whose experience and training have been approved by the appropriate government agency authorized to license the use of radionuclides.

Note: Macrotec (Aggregated Albumin [Human]) is not radioactive. However, after ^{99m}Tc is added, adequate shielding of the resultant preparation should be maintained.

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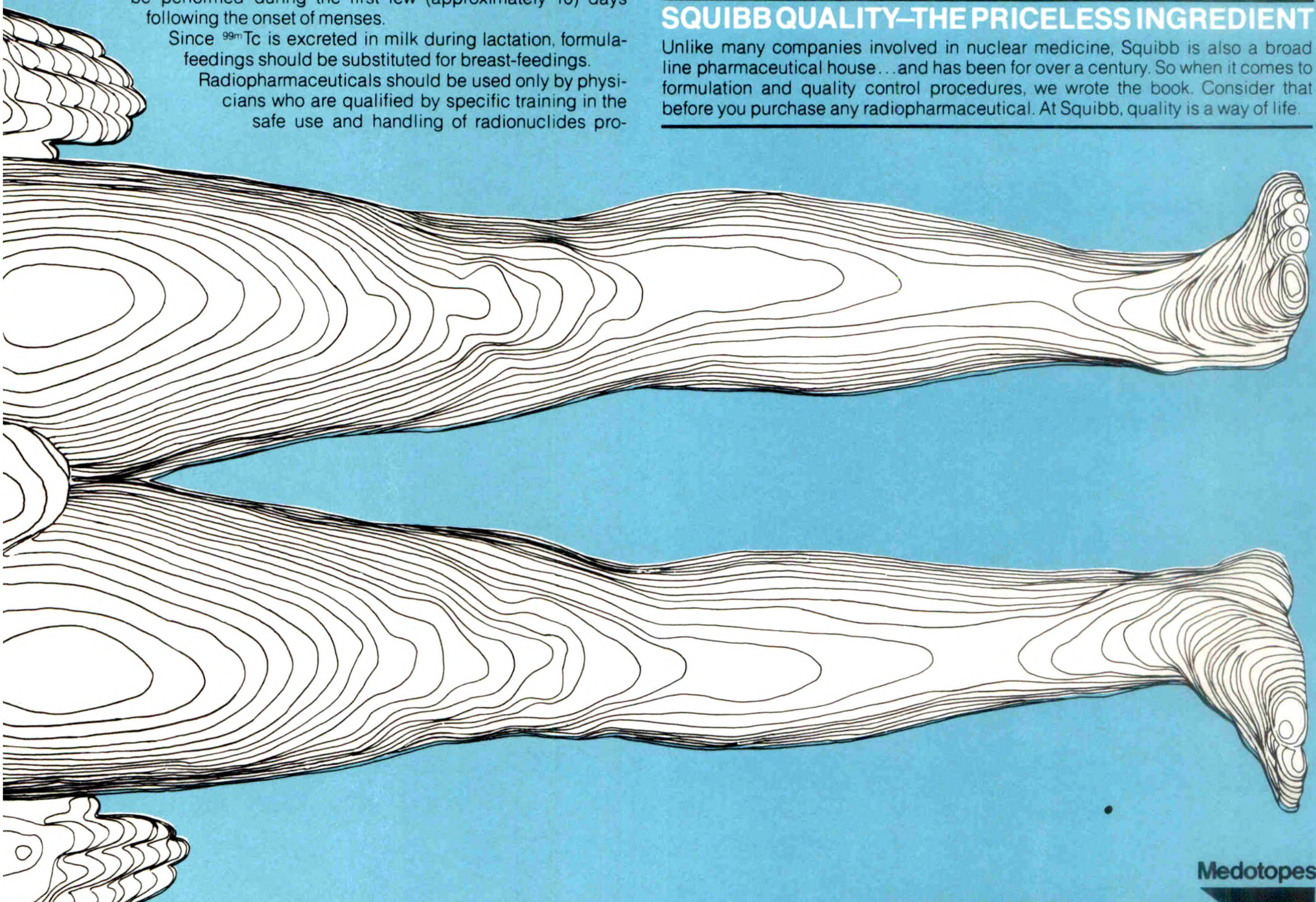

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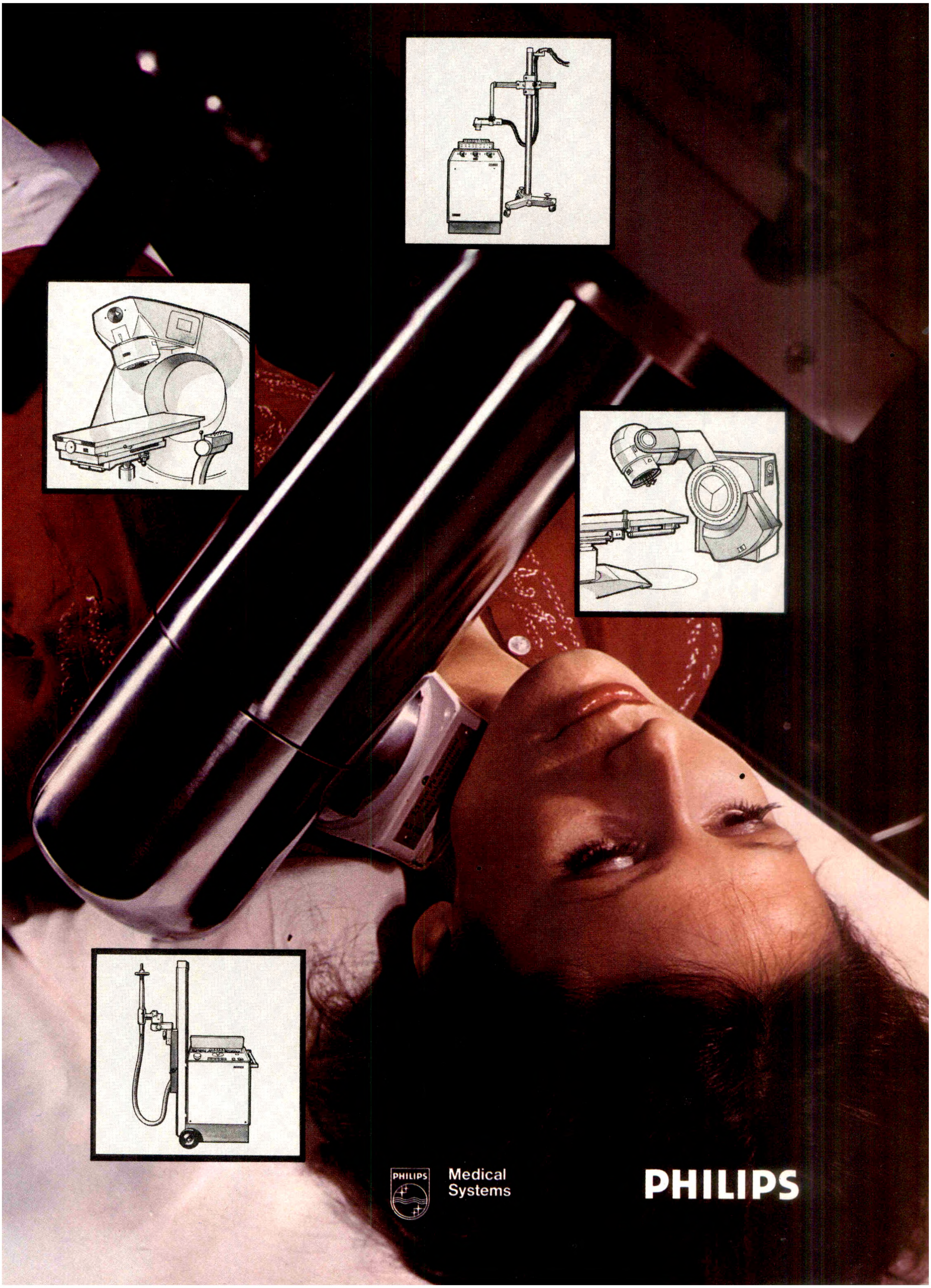
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VICTOR A. MARCIAL
PRESIDENT, 1975
AMERICAN RADIUM SOCIETY

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THE ROLE OF THE CLINICIAN IN COMMUNITY CANCER CONTROL ACTIVITIES*

By VICTOR A. MARCIAL
SAN JUAN, PUERTO RICO

IT is indeed a privilege and honor to have been afforded the opportunity of serving as president of the American Radium Society during the past year and to be allowed to present to you the presidential address of this, the 57th annual scientific meeting of our organization. Needless to say, this is an occasion when presidents express some of their philosophical views on how things have been and how things should be.

In analyzing the content of the past 11 presidential addresses, I note a constant preoccupation with the cancer patient and the services rendered to him. This is to be expected from a society constituted mainly of clinicians who are not satisfied with what is presently achieved in the field of cancer therapy. The reason we come to these meetings is largely due to dissatisfaction with the yield from our therapeutic efforts.

I myself have felt and continue to feel this dissatisfaction. In October of this year it will be 20 years since I completed my training in therapeutic radiology and began work in Puerto Rico. During these 20 years I have been exposed to diverse experiences which provide the basis for my remarks today. Needless to say, my experiences may differ somewhat from those of others in the audience. Here in Puerto Rico we are in a different "ball park." Our community has been and continues to be economically underdeveloped; the average income is less than half of that found in the poorest state on the U.S. mainland. However, in spite of this economic limitation, Puerto Rico has proven to be a fascinating island-wide laboratory for the study of cancer. It is a well-defined geographical area with a population of three million people, mainly of Spanish ancestry; the present median age is 21 years. This island laboratory will be constantly increasing in value for the study of all aspects of cancer; in particular, it will be suitable for study of the impact of environmental changes such as urbanization, power production, and overpopulation.

Our experience has taught us lessons which may be of value to people in other places. One of the most important is the realization that clinicians must become involved with what happens to the cancer patient outside of their institutions. It is not enough to develop adequate departments with optimal interdepartmental relationships and multidisciplinary management for the care of the patient at the institutional level. This has no effect on what happens to the patient before and after his treatment. Community involvement by clinicians in cancer control activities should be multidirectional.

The clinician must know the magnitude

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* Presidential address presented at the Fifty-seventh Annual Meeting of the American Radium Society, San Juan, Puerto Rico, May, 1975.

From the Puerto Rico Nuclear Center, Caparra Heights Station, and the University of Puerto Rico School of Medicine, San Juan, Puerto Rico.

of the cancer problem in the community, both quantitatively and qualitatively. In Puerto Rico we have achieved this through a computerized cancer registry which contains registration and follow-up information on over 80,000 cancer patients diagnosed since 1950. All persons with a histological diagnosis of cancer or clinical diagnosis of the disease at time of death are registered. Reported deaths from cancer and all other causes are cleared through the Registry as a means to achieve follow-up.

The Registry has shown that crude cancer incidence and mortality rates have doubled from 1950 to 1972. Still, in view of our young population, they represent only two-thirds of what is found on the mainland. The increase in incidence has been equal in both sexes, but mortality has been more notable in males than in females. The 10 most commonly observed sites in females, in order of frequency for the year 1972 (the last year completed), were uterine cervix, skin, breast, stomach, body of uterus, colon, rectum, bone marrow, ovary, and mouth. The most frequent sites in men for the same time period were skin, prostate, stomach, oral cavity, lung, esophagus, pharynx, bone marrow, urinary bladder, and colon.

Age-adjusted analyses of the evolution of cancer in Puerto Rico also reveal a continuous increase in the general incidence as well as the incidence for some specific sites. Sites such as stomach and esophagus seem to be declining in frequency. Besides differing from the mainland in total cancer incidence, Puerto Rico has notable site differences compared to the continent. Cancer of the oral cavity, pharynx, and esophagus are several times more frequent in Puerto Rico, whereas cancer of the lungs and breast show less than half the incidence found on the mainland.

The Registry shows that only 30% of cancer patients receive therapy at the two specialized oncology institutions in Puerto Rico, while 70% are treated at general hospitals.

Except for selected sites such as the cervix, the curability from cancer in Puerto Rico, as judged from survival figures in our registry, is lower than in the rest of the nation. This is in part a reflection of the advanced state of the tumor when the patients receive therapy. For 1972, the Registry data show that 22% of cancer in women and 31% of cancer in men went untreated. This was primarily due to the advanced stage of the disease. Our radiation therapy department, presently the most important contributor of patients to the protocols of the Radiation Therapy Oncology Group, has registered predominantly advanced stages.

These facts illustrate the need for community services for the patient, particularly cancer education. Our patients are frequently unaware of important symptoms and signs that may be related to cancer; some may not go to the physician because they are afraid of being told they have cancer. Neither are our physicians free of fault. Many persist in treating a condition as a benign process in spite of the presence of obvious malignancy.

In a community such as ours, the cancer clinician must accept the challenge of involving himself in what happens outside his institution. Until now the main routes for this involvement have been the cancer program of the Puerto Rico Department of Health and the Puerto Rico Division of the American Cancer Society, established here less than 2 years ago. A promising new development is the creation of a Comprehensive Cancer Center as a joint effort of the medical sciences campus of the University of Puerto Rico, the Puerto Rico Department of Health, and other community institutions. Federal funding for this cancer center will begin on July 1, 1975. We foresee that this cancer center will eventually evolve into a cancer management system for the entire island, integrating the efforts of government, the academic sector, and private institutions.

A significant part of our involvement with the community has been in the area of cancer detection. Needless to say, the outcome in asymptomatic patients with cancer is more promising than when symptoms develop which cause the patient to seek a physician. In Puerto Rico the latter situation has resulted in low 5 year survival rates.

We have concentrated our efforts in cancer detection on cancer of the cervix, since it accounts for one of every four malignant tumors in women of all ages and one in two for the 35–40 year age group. Vaginal cytology has been established in every district of our Island; nearly 200,000 examinations are performed each year. The last published report on this effort, based on close to one-half million women examined, showed 3.5 cases per 1,000 initially screened dropping to 0.5–0.8 per 1,000 subsequent examinations. Based on Registry data, 50% of cases with diagnoses of cervical cancer are now in the *in situ* category compared to 5% of the cases registered in 1950. In addition, the percentage of Stage 1 cases among the invasive category has increased significantly as observed in clinical practice. A 60% reduction in mortality from cancer of the uterus has been observed from 1950 to 1970.

Detection efforts for sites other than the cervix have not been as active or as effective. Detection of breast cancer, which has shown a threefold increase in incidence since 1950, has been limited because of difficulty in obtaining mammographic studies at a reasonable cost for the poor and lower middle class population groups. In the past year the Puerto Rico Division of the American Cancer Society began conducting mass screening for breast cancer and began demonstration detection clinics for other sites. Needless to say, these activities must be established on a regular basis and should be comprehensive in scope. Ideally every adult patient should have access to a routine physical examination once a year.

Tumor clinic conferences in general hospitals, when attended by experienced cancer clinicians, have been found useful in providing a multidisciplinary consultation service to patients. Presently we have seven tumor clinic conferences in the San Juan metropolitan area; five meet once a week, one has monthly meetings, and one meets twice a week. I feel confident that when the Comprehensive Cancer Center becomes fully operational, these tumor conferences will increase in number and frequency. Ideally we would like to have this consultation service available to all cancer patients in the community.

Cancer education of physicians has been another of our concerns in the community. How to reach the very busy medical practitioner is a problem everywhere. For years we have provided physicians in Puerto Rico with publications on clinical cancer. Last year we initiated an annual postgraduate course for practitioners jointly sponsored by the Puerto Rico Division of the American Cancer Society, the Puerto Rico Department of Health, and the University of Puerto Rico School of Medicine. We expect that the Comprehensive Cancer Center in the future will become the main provider of continuing cancer education for our physicians in collaboration with the other agencies mentioned. We must improve our methods for motivating busy practitioners. We must give them the opportunity to become involved with cancer patients in the early stages of the disease. We must promote their participation. After all, the average physician in Puerto Rico will see no more than two or three new cancer cases per year. Compared to the dozens of cases seen at a busy oncology department, this is not enough to develop adequate clinical experience.

Public education on cancer in Puerto Rico continues to be an area of great need. The Department of Health has carried on a program for many years, but it is hard to assess its impact. In the last 2 years the Puerto Rico Division of the American Cancer Society has promoted public educational activities. Present needs are for basic information on cancer for school-age children and for adult education on symptoms and signs, the need for early diagnosis and treatment, and the need to practice prevention on those forms of cancer which are preventable. Again the Comprehensive Cancer Center may prove to be a valuable tool for improving public education in Puerto Rico.

Rehabilitation services for cancer patients on our Island have been almost nonexistent until the Puerto Rico Division of the American Cancer Society began its operation 2 years ago. Now we are providing help to patients with mastectomy, laryngectomy, colostomy, and amputations. In addition, an orientation and guidance program for parents of children with cancer has been very successful.

I have mentioned several times the Puerto Rico Comprehensive Cancer Center. This is more than a physical installation, it is an operational concept which should join and coordinate all the cancer efforts in our community. We trust that eventually it will become the most useful tool or channel for the involvement of cancer clinicians in the community. I envision it as the means for bringing the latest cancer knowledge to our community and for generating knowledge for our benefit and for the benefit of others outside Puerto Rico.

In summary, the cancer clinician must play a leading role in the development and operation of community cancer control activities, which will help in reducing mortality and morbidity from this disease. Involvement in these activities can be very rewarding; the channels for involvement exist or can be created in all communities.

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RADIATION THERAPY FOR TESTICULAR TUMORS METASTASIZING TO THE LUNGS*

By THEODORE C. M. LO, M.D.,† *and* YUNG H. SON, M.D.
NEW HAVEN, CONNECTICUT

ABSTRACT:

Records of 63 cases of testicular tumors treated at the Hunter Radiation Therapy Center, Yale-New Haven Hospital from 1962 through 1971 were reviewed. One hundred percent cure rate was obtained in the 36 Stage I and II pure seminoma (Group I) patients. For Stage I, the para-aortic and homolateral iliac lymph nodes were irradiated to a dose of 3,000 to 3,500 rads in three to four weeks. Elective irradiation of the mediastinum and supraclavicular areas was omitted. For Stage II, such extended field irradiation was employed to a dose of 2,000 to 3,000 rads in two to three weeks.

Six (or 43 percent) of the 14 embryonal carcinoma (Group II) patients are alive for a minimum of three to a maximum of eleven years. Both teratoma (Group III) patients are alive at five and seven years as well. All eight Stage I teratocarcinoma (Group IV) patients are alive with no evident disease at three to ten years.

Our data indicate the difference in prognosis between patients who subsequently developed localized lung metastases and those who initially presented with pulmonary disease. We conclude that intensive combined efforts of both radiation and medical oncologists can salvage a considerable number of patients with metachronous onset of pulmonary metastases.

ALTHOUGH testicular tumors comprise less than one percent of all male neoplasms, they constitute the fourth leading cause of all cancer deaths in the 15 to 34 year age group in men.[16] The majority of testicular tumors are of germ cell origin and over 90 percent of them are malignant.[15] The mode of speed *via* the lymphatic system is well recognized: first to the para-aortic and iliac chains, then to the supraclavicular lymph nodes. Blood-borne metastasis may take place early in the course of the disease, particularly in such biologically aggressive tumors as choriocarcinoma. However, tumor cell migration to the blood stream is perhaps more likely to occur through the lymphatic system causing early deposits in distant organs.[18]

For the past decade, the advances in radiation therapy and chemotherapy, and above all, the advent of combined therapy have contributed considerably to the improved cure rates.[1-4,7,9,10,11,13,14,17,19,20] A significant number of patients has been salvaged by elective extended nodal irradiation to sites at risk, and a lesser number by early detection and institution of aggressive combination therapy for distant metastasis.[9,12,19]

Treatment for pulmonary metastases has indeed become a challenge to both the radiation and medical oncologists. In a recent study, van der Werf-Messing[19] found no cure in seven patients who received whole lung irradiation (WLI) for diffuse pulmonary metastases as an initial presentation. Neither did she observe any salvage in 17 patients who had localized pulmonary metastases treated by "triple" chemotherapy with chlorambucil, actinomycin D and methotrexate. However, 50 percent of her 15 patients with localized lung metastases were alive and free of disease at 30 months after WLI followed by actinomycin D.

Prompted by this report, we reviewed our

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TABLE I

CLASSIFICATION*

Group I	Seminoma, pure
Group II	Embryonal carcinoma, pure or with seminoma
Group III	Teratoma, pure or with seminoma
Group IV	Teratoma with either embryonal carcinoma, choriocarcinoma, or both, and with or without seminoma
Group V	Choriocarcinoma, pure or with either seminoma or embryonal carcinoma, or both

* Dixon, F. J. and Moore, R. A. Tumors of male sex organs. Atlas of Tumor Pathology, section VIII, fascicle 31b and 32. Armed Forces Institute of Pathology, Washington, D. C., 1952.

experience with testicular tumors treated at the Hunter Radiation Therapy Center of the Yale-New Haven Hospital from 1962 through 1971. The aim of this study is to assess over-all survival of the germinal tumors of various histologic types and stages, with particular interest in the outcome of the patients with pulmonary metastases.

MATERIAL AND METHOD

Records of 63 patients with either seminoma or carcinoma of the testis were reviewed. All but two received postoperative radiation therapy and all were followed for a minimum of three years. Of the two patients who did not receive radiation therapy: one with Stage I$_{\text{A}}$ teratocarcinoma was last seen without evidence of disease at four years following negative retroperitoneal lymph node dissection, and the other with Stage I$_{\text{A}}$ pure teratoma is currently alive and well at five years, without any form of therapy after orchiectomy.

The Dixon and Moore[6] pathological classification and a modified Walter Reed General Hospital staging system[12] were adopted in this review, as shown in Tables I and II, respectively. Table III shows the distribution of the 63 patients by stage and histology.

At Yale, all patients were treated either with a 2-MeV van de Graaff generator or a 6-MeV Varian linear accelerator. The treatment technique and tumor dose were uniformly standardized in Stage I and II seminomas. Stage I patients received 3,000 to 3,500 rads in three to four weeks to the homolateral iliac chain and the para-aortic lymph nodes up to the level of the diaphragm. With Stage II patients, additional treatment was given to the mediastinum and both supraclavicular fossae with a dose of 2,000 to 3,000 rads in two to three weeks. We have been including the right supraclavicular fossa in the treatment portals because right-sided thoracic duct drainage is now a well recognized normal variation.[5,8] Since 1968, both anterior and posterior fields were treated daily. On the other hand, treatment policies for non-seminomatous testicular tumors varied rather considerably, but in general, higher doses were used, with or without prior retroperitoneal lymph node dissection.

Nine patients received pulmonary irradiation for lung metastases. The doses are described in Tables V and VI. Whenever WLI was given, both left and right lungs were treated simultaneously without correction for tissue inhomogeneity. All patients were treated five times per week and none received any kind of chemotherapy concurrently with pulmonary irradiation.

RESULTS

All recurrences appeared within 30

TABLE II

STAGING SYSTEMS*

I$_{\text{A}}$	Tumor confined to one testis. No clinical nor roentgenographic evidence of spread beyond
I$_{\text{B}}$	Histologic evidence of metastases to iliac or para-aortic lymph nodes present at time of retroperitoneal dissection
II	Clinical or roentgenographic evidence of lymph node metastases below the diaphragm
III	Clinical or roentgenographic evidence of lymph node metastases above the diaphragm
IV	Clinical or roentgenographic evidence of distant metastases beyond the lymphatic system

* Adopted from Maier, J. G., Sulak, M. H. and Mittemeyer, B. T. Seminoma of the testis: analysis of treatment success and failure. AM. J. RÖNTGENOL, RAD. THERAPY & NUCLEAR MED., 1968, *102*, 596–602.

months after diagnosis. Fifty-one (81 percent) of the 63 patients are currently alive and well (Table IV).

Thirty-five of the 36 Group I patients with Stage I and Stage II disease are at present alive with no evidence of disease (NED). A sixty year old man with Stage I disease died of pulmonary failure at four years and was found to have squamous cell carcinoma of the lung on autopsy without evidence of recurrent seminoma.

Six of the 14 Group II patients are alive and five of the six are alive with NED. The remaining survivor was staged as IV because of a positive bone scan alone.

There were two Group III patients. Both are alive with NED at five and seven years.

Eight of the nine Group IV patients had Stage I disease and all of them are alive with NED at present. The one Stage IV patient was dead at eight months.

No Group V patient was encountered in this series.

During the ten year period of this study, five Stage IV patients with pulmonary metastases received WLI with a dose range of 1,700 to 2,100 rads in 14 to 23 days (Table V). There was no correction for lung transmission. Three of the five patients received additional boost-dose irradiation. Another patient developed recurrent chest symptoms and received a repeated course of WLI. Three patients also received chemotherapy. All five patients were dead at two years with persistent pulmonary disease. No complication from pulmonary irradiation was observed.

Table III

DISTRIBUTION OF PATIENTS BY STAGE AND HISTOLOGY

Group	Stage				Total
	I$_A$	I$_B$	II	IV	
I	22	0	14	2	38
II	3	4	3	4	14
III	2	0	0	0	2
IV	6	2	0	1	9
Total	33	6	17	7	63

Table IV

SURVIVAL AT THREE YEARS

Group	Stage				Total
	I$_A$	I$_B$	II	IV	
I	22/22*	/0	14/14	0/2	36/38
II	1/3	2/4	2/3	1/4†	6/14
III	2/2	/0	/0	/0	2/2
IV	6/6	2/2	/0	0/1	8/9
					52/63

* One patient died from intercurrent disease at 4 years.

† Survivor had positive bone scan but negative metastatic series.

All other patients are with NED at present.

In contrast, two of the four Stage I Group II patients who received chemotherapy and pulmonary irradiation for subsequent onset of lung metastases are at present alive with NED (Table VI). These two cases are described below.

REPORT OF CASES

Case I. F.B., a 30 year old man, entered his local hospital on August 18, 1967 with a few weeks' history of a mass in his right scrotum. Chest roentgenograms and intravenous pyelograms were negative. A right orchiectomy was performed and the histology was embryonal carcinoma. About a week later a retroperitoneal lymph node dissection was carried out and the lymph nodes at the level of the renal vessels were found to be involved by tumor. He then received radiation therapy to the right lower quadrant of his abdomen and the lower para-aortic area to a dose of 4,100 rads in 37 days, and the upper para-aortic area and the mediastinum to a dose of 4,000 rads in 40 days, followed by left supraclavicular irradiation to 3,700 rads in 22 days ending on January 10, 1968. In March, he developed acute abdominal pain and at laparotomy bowel obstruction was found secondary to adhesions which were freed. The postoperative course was complicated by wound infection which was eventually resolved. Follow-up chest roentgenograms in May of 1968 revealed lung nodules which were found to be enlarging a month later. He

TABLE V

STAGE IV PATIENTS WHO RECEIVED WHOLE LUNG IRRADIATION

	Group	Dose to Whole Lung ("boost" dose)	Chemotherapy	Additional Treatment for Recurrent Chest Symptoms	Died at
R.W.	II	2,000 rads/14 days	Refused	2,000 rads/14 days	22 mo.
F.V.	II	2,100 rads/16 days	Chlorambucil Actinomycin D Methotrexate	Mediastinum 1,000 rads/5 days	7 mo.
J.B.	I	2,000 rads/14 days (RL 1,400 rads/10 days)	None		2 mo.
S.S.	II	1,770 rads/22 days (RLL 1,200 rads/4 days)	Cyclophosphamide Actinomycin D		17 mo.
T.N.	IV	1,700 rads/23 days (LLL 2,600 rads/15 days)	Cyclophosphamide Vincristine Actinomycin D		8 mo.

RL = Right lung.
RLL = Right lower lobe.
LLL = Left lower lobe.

was then referred to the medical oncology service of the VA Hospital in West Haven and was started on chlorambucil 8 mg twice a day. A six week course resulted in no response in the pulmonary disease and he was switched to vinblastine in September, 1968. Initially regression of the metastatic lesions was noted but in May of 1969 recurrence was apparent in the upper and lower lobes of the left lung. Vinblastine was discontinued. The patient was then given a five day course of actinomycin D, 15 mcg/kg per day. Two months later, in July, 1969 chest roentgenograms showed persistence of these lesions and local irradiation was begun at the Yale-New Haven Hospital. Two thousand, six hundred rads (2,600 rads/four fractions/six days; 5×5 cm^2 fields) were given to the left upper and lower lobe nodules. The patient has had no further therapy since and he is now living with NED.

CASE II. S.B., an 18 year old college student underwent a right orchiectomy on October 9, 1969 after a testicular mass was discovered on a routine physical examination. The lesion was interpreted as seminoma mixed with embryonal elements on microscopic section. Chest roentgenograms, intravenous pyelograms and lymph-

TABLE VI

STAGE I EMBRYONAL CARCINOMA PATIENTS (GROUP II) WHO LATER DEVELOPED PULMONARY METASTASES

	Initial Stage	Dose to Whole Lung ("boost" dose)	Current Status	Survived after Orchiectomy
D.M.	I_B	1,800 rads/7 days	Dead; pulmonary metastases	Less than 1 year
L.W.	I_A	(LLL only 4,100 rads/18 days)	Dead; pulmonary metastases	2 years
F.B.	I_B	(LUL and LLL 2,600 rads/6 days)	N.E.D. (see text)	7 years
S.B.	I_A	1,800 rads/17 days (RLL 500 rads/1 day 1,000 rads/1 day)	N.E.D. (see text)	5 years

LLL = Left lower lobe.
LUL = Left upper lobe.
RLL = Right lower lobe.
N.E.D. = No evidence of disease.

angiograms were negative. He then received radiation therapy to the para-aortic and right iliac areas to a dose of 4,460 rads in 36 days followed by mediastinal and supraclavicular irradiation to a dose of 2,600 rads in 16 days at the Hunter Radiation Therapy Center of the Yale-New Haven Hospital. In April of 1970, follow-up chest roentgenograms showed lung nodules. The patient was asymptomatic. Three courses of chemotherapy were given without avail. The first course consisted of cyclophosphamide 1 gram/M^2 and vincristine 1.4 mg/M^2. The second course consisted of actinomycin D, 10 mcg/kg, and vincristine, 1.4 mg/M^2. The third course consisted of cyclophosphamide, 1 gram/M^2, followed by vincristine, 1.4 mg/M^2 per day for two days, ending on July 21, 1970. Persistence of the right lower lobe lesion was apparent and on August 12, 1970 the patient was started on right and left lung irradiation to 1,800 rads in 17 days followed by boost-dose of 500 rads in one treatment to the right lower lobe. On October 9, 1970 the patient was again given cyclophosphamide, 1 gram/M^2 and on the next day vincristine, 1.4 mg/M^2. In November, actinomycin D, 10 mcg/kg per day, was given for four days followed by vincristine, 1.4 mg/M^2 intravenously on day five. However, chest roentgenograms taken later in the month showed that the right lower lobe nodule had increased in size and a new lesion was noted in the vicinity. On November 19, 1970, 1,000 rads were given to the right lower lobe in a single treatment. In December the patient was started on mithramycin. Follow-up chest roentgenograms in February of 1971 showed an "infiltrate" in the right middle and lower lobes, and right middle and lower lobectomy was performed in February, 1971. The surgical specimen revealed only radiation fibrosis without tumor. Subsequently the patient received two further courses of mithramycin. Since May of 1971 he has received no further treatment and he is now living with NED.

DISCUSSION

After reviewing our data, we concur with Smithers *et al.*[17] that death from pure seminoma is unexpected today. It results only when dissemination has already taken place prior to initiation of therapy. Cure rates for the non-seminomatous tumors are also rising due to the advances in radiation therapy and chemotherapy during the past decades.[9,15,17] Our over-all survival rates compare favorably with those of other recent series.[2,3,7,9,13,14,17]

Studies from Walter Reed Hospital,[4] University of California Medical Center in San Francisco[20] and Rotterdam Radiotherapy Institute[19] indicated the potential cure from pulmonary metastases by combination WLI and chemotherapy. However, the ultimate prognosis was apparently different in those who subsequently developed localized lung metastases from those who initially presented with diffuse pulmonary disease.[19]

Cox *et al.*[4] irradiated eleven patients, with or without concomitant actinomycin D. Nine of them were dead at two years with persistent or recurrent lung disease. Wharam *et al.*[20] reported three survivors among seven patients with metastatic embryonal or teratocarcinomas treated by WLI and combination chemotherapy of actinomycin D, cyclophosphamide, vincristine, and mithramycin. However, the duration of follow-up was short, with the longest survivor living at 31 months. On the other hand, van der Werf-Messing[19] observed that 50 percent of her 15 patients with localized pulmonary metastases from malignant teratoma survived free of disease at a minimum of 30 months. Her patients received WLI to a dose of 3,000 rads in four weeks followed by a boost-dose to the visible lesions. There was a four week interval between completion of radiation therapy and administration of actinomycin D. The complication rate, however, was as high as 33 percent.

Although the case number is relatively small, our experience at Yale is similar to that of van der Werf-Messing's. While all five Stage IV patients with pulmonary disease were dead by the end of two years despite radical therapy, two (50 percent) of the four Stage I embryonal carcinoma patients with subsequent development of pulmonary metastases were salvaged by chemotherapy and lung irradiation. However, the radiation doses we gave were lower than those reported by van der Werf-Messing[19] and none of our patients developed radiation pneumonitis.

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RADIATION THERAPY IN THE TREATMENT OF GLIOBLASTOMA*

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ABSTRACT:

A retrospective study of 127 cases irradiated for glioblastoma was made to assess the role of radiation therapy and to determine the optimal technique of radiation therapy.

The over-all survival rates of our series were 52 percent at one year, 19 percent at three years, and twelve percent at five years after radiation therapy.

Survival time of the patients is influenced by various factors other than treatment: age, sex, histologic grading, duration of symptoms, and location of tumor. Among these factors, the location of the tumor was the most important in our present series.

Surgical treatment can extend the survival time. More extensive resection results in longer survival, provided that the location of the tumor allows such a surgical procedure.

Radiation therapy can prolong the survival time of those with glioblastoma, but a high tumor dose of more than 6,000 rads or 1,700 rets is necessary to improve the prognosis significantly. Therefore, irradiation should be administered through generous fields according to the extent of the tumor under precise planning to determine the accurate localization and extent of the tumor.

GLIOBLASTOMA multiforme is recognized as the most malignant of the various intracranial neoplasms. Its incidence is the highest of all malignant gliomas in nearly every large series of cases.[2,7,14,20] In spite of the advances of neurosurgical technique, results of surgical treatment indicate that the majority of glioblastomas cannot be extirpated completely and recur sooner or later, because of their highly infiltrative character.[6,14,16] Consequently, radiation therapy has been used widely as an adjunct to surgical treatment of this disease. However, conflicting views exist at present on the value of irradiation in the treatment of glioblastoma.

Effects of radiation therapy for glioblastoma are determined mainly on the basis of three criteria: (1) histopathological change of the irradiated tumor; (2) clinical improvement of the patient; and (3) length of survival after irradiation. Most histologic studies reveal residual tumor cells following radiation therapy.[2,17,30] Peirce and Bouchard[18] reported that, in a series of 130 patients who were irradiated with tumor doses ranging from 6,500 to 7,500 rads, tumor cells were found at the site of primary neoplasm in all of 54 cases reoperated or autopsied. Zülch[30] stated that glioblastoma was a tumor of limited radiosensitivity and there was only relative indication for irradiation in the treatment of this tumor. However, it is very difficult to assess the effect of irradiation on the basis of histologic damage in tumor cells. Serial biopsies are usually impossible due to the intracranial location of these masses. When the biopsy material is examined histologically, the amount of tissue changes which may be attributable to radiation therapy cannot always be differentiated from necrosis and

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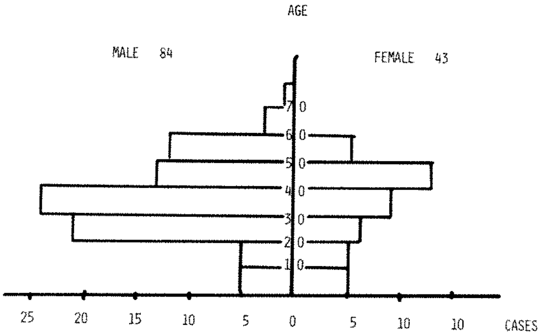

Fig. 1. Age and sex distribution of 127 patients irradiated for glioblastoma from 1955 to 1972.

vascular change which occur spontaneously in the non-irradiated tumors. Furthermore, the viability of the residual tumor cells cannot be determined from their morphology with any degree of certainty.

Although several authors state that the combined use of surgery and irradiation result in improvement of the clinical symptoms and prolongation of the survival,[6,7,25,27] it is difficult to separate the contributions of surgery from those of irradiation. Most authors reported longer survival time among those who received radiation therapy after surgery than those treated by surgery alone. However, there have been few reports which could elucidate the quantitative relation between survival time and radiation techniques, for example dose-survival relationships. Such unsettled results may be attributable to the extremely poor outcome and the influence of many prognostic factors other than radiation therapy. Therefore, the real value of irradiation in the treatment of glioblastoma has not yet been established.

A retrospective study on the survival time of 127 cases treated in our department was made to analyze various factors relating to the prognosis of patients with glioblastoma, as well as adequate dose and volume of irradiation for this tumor.

CLINICAL MATERIAL

Over a period of 18 years from 1955 to 1972, 557 patients with various brain tumors were treated by irradiation in the Department of Radiology of Kyoto University Hospital. Three hundred and thirty-seven cases (60.3 percent) were classified as glioma and 127 (22.8 percent or 37.8 percent of all gliomas) as glioblastoma (astrocytoma Grade III and IV). One hundred and sixteen cases were referred to our department after surgical resection, five following biopsy and six following shunt operation. Histology was verified later by autopsy or reoperation in the last six cases.

Our series consisted of 84 males and 43 females (Fig. 1). The youngest patient was a four year old boy with a tumor of the pons, and the oldest was a 72 year old man with a tumor of the left parieto-occipital lobe. The average age in our series, 35.4 years, was rather younger than that reported by other authors.[20,25,28] However, the incidence of glioblastoma among children under the age of 15, 10.5 percent or 15 of 143 children with various brain tumors, was markedly lower than that among adult patients, 27.1 percent or 112 of 414 patients.

The glioblastoma was located in the mid-brain or brain stem in 13 cases, of which eight were children, and in the cerebrum in 114 cases. No difference in incidence was observed between the cerebral hemispheres (Table I).

Table I

LOCALIZATION OF GLIOBLASTOMA IN 127 PATIENTS

Location	Right	Left	Bilateral	Total
Frontal	23	18	7	48
Fronto-parietal	7	7	—	14
Parietal	4	5	—	9
Parieto-temporal	1	2	—	3
Temporal	13	12	—	25
Temporo-occipital	2	1	—	3
Parieto-occipital	3	5	—	8
Occipital	—	2	—	2
Lateral ventricle	1	1	—	2
Midbrain				8
Brain Stem				5
Total	54	53	7	127

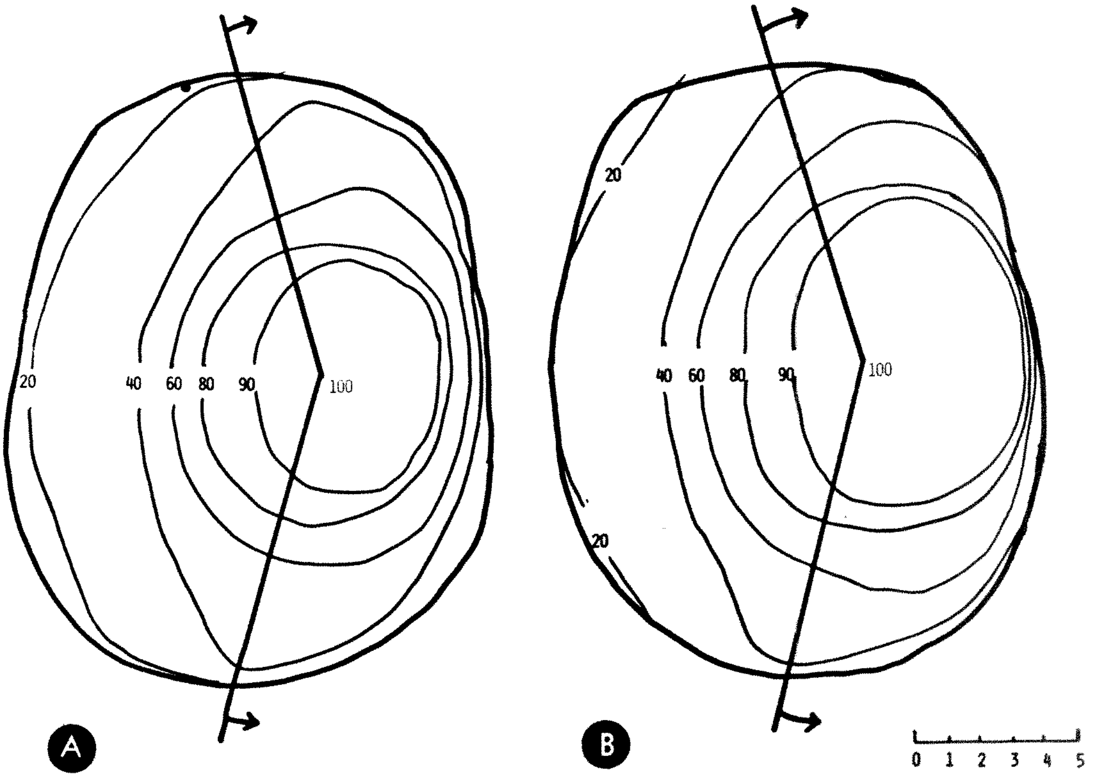

Fig. 2. Isodose distribution (percent of axial depth dose) obtained in 210° arc therapy with ^{60}Co γ-ray (*A*) For field size of 8×6 cm. Volume irradiated with dose over 80 percent of axial dose is about 450 cc. (*B*) For 10×8 cm field. Eighty percent volume about 800 cc.

RADIATION THERAPY

The program of radiation therapy consisted of a single protracted course of irradiation with 200 kV x-ray in 37 cases treated prior to 1962, and with ^{60}Co γ-ray in the remaining 90. Various levels of tumor dose were used, but the planned dose range was 5,000 to 6,500 rads over five to eight weeks in most cases. In 27 cases, radiation therapy was discontinued before the tumor dose reached 5,000 rads, because of side effects or for other reasons. The tumor dose in our present series averaged 5,285 rads (S.D. 1,623) and the nominal standard dose[5] 1,501 rets (S.D. 380). At the onset of treatment, a small daily tumor dose of 50 to 100 rads was delivered over three to five days; subsequently tumor doses were gradually increased to 180 to 200 rads per day or 900 to 1,000 rads per week.

There is some controversy as to the choice of the size of treatment fields in the radiation therapy of gliomas. Although some radiologists[4,12] preferred to irradiate nearly the entire cranial vault, more limited fields have been used in our present series. In general, irradiation was delivered through a generous field according to the extent of tumor, determined on the basis of radiographic findings, isotope studies and surgical reports. Multiple ports or two opposing fields were used in some cases, but 210° arc therapy with field widths ranging from 6 to 8 cm was used in most cases (Fig. 2). The volume irradiated with more than 80 percent of the axial dose was about 450 cc with 8×6 cm portals and about 800 cc with 10×8 cm portals.

RESULTS

Eleven of 127 patients were alive at the end of 1974, and six of the living cases survived five to 13 years after radiation ther-

Table II

SURVIVAL RATES ACCORDING TO AGE AT RADIATION THERAPY

Age		Under 15 yr.	16–35 yr.	Over 36 yr.	Total
No. of Cases		15	46	66	127
Average Tumor Dose		5,051 rads	5,306 rads	5,314 rads	5,285 rads
Standard Deviation		1,898	1,578	1,658	1,623
Percent Survival	6 mo.	47*	79*	77*	74
	1 yr.	33	57	52	52
	2 yr.	13	38	27	29
	3 yr.	7	31*	13*	19
	4 yr.	7	23	6	13
	5 yr.	7	20	6	12

* $p < 0.05$ between figures.

apy. Life expectancy from the first day of radiation therapy was calculated by the life table method. No allowance was made for correction on account of death by accident or unrelated disease.

Over-all survival rates of our series were 52 percent at one year, 19 percent at three years, and twelve percent at five years after radiation therapy (Table II). Survival rates were analyzed under the following items; age, sex, duration of symptoms, location of tumor, and dose and field size of radiation therapy.

Age at radiation therapy: Our series consisted of 15 children (under 15 years of age), 47 younger patients (16 to 35 years old) and 67 older patients (over 36 years of age). No significant difference in the average tumor doses was noted among these three groups, but there was a marked difference in the survival rates according to age (Table II). Children carried the most unfavorable prognosis, and their six months' survival rate, 47 percent, was significantly lower than that of the other two groups. The prognosis of the younger group was rather favorable with a statistically significant difference of three years in comparison with the other two groups.

Sex: No significant differences were noticed between males and females in regard to the survival rates, average tumor dose, and location of the tumor (Table III).

Duration of symptoms: Mean duration of symptoms prior to the surgical treatment was 7.5 months and median duration 3.5 months in our present series. According to the duration, our cases were divided into three groups: less than three months, three to six months, and more than six months. The groups comprised 51, 40, and 36 cases, respectively. Duration of symptoms bore an inverse relationship to survival (Table IV). In particular, the two year survival rate in the patients with symptoms longer than six months, 45 percent, was significantly higher than in those with shorter duration.

Tumor location: Intracranial location of the tumor substantially affects the prognosis. None of those with a deep or bilateral tumor survived three years after radiation therapy (Table V). Among patients whose

Table III

SURVIVAL RATES ACCORDING TO SEX

Sex		Male	Female
No. of Cases		84	43
Average Tumor Dose		5,318 rads	5,224 rads
Standard Deviation		1,528	1,822
Percent Survival	6 mo.	74	74
	1 yr.	50	56
	2 yr.	30	28
	3 yr.	18	21
	4 yr.	12	14
	5 yr.	10	14

Table IV

SURVIVAL RATES ACCORDING TO DURATION OF SYMPTOMS

Duration of Symptoms		Under 3 months	3–6 months	Over 6 months
No. of Cases		51	40	36
Average Tumor Dose		5,261 rads	5,327 rads	5,392 rads
Standard Deviation		1,433	1,589	1,295
Percent Survival	6 mo.	75	70	78
	1 yr.	51	48	58
	2 yr.	20*	26*	45*
	3 yr.	12	21	25
	4 yr.	7	16	16
	5 yr.	7	16	13

* $p < 0.05$ between figures.

tumors arose from a cerebral hemisphere, the prognosis of those with right-sided tumor was more favorable than that of those with left-sided tumor. The differences of survival rates between the latter two groups were statistically significant at two and three years after treatment (Table VA). Furthermore, those with tumors located in the right frontal lobe carried the most favorable prognosis and 33 percent of them survived five years (Table VB).

Radiation dosage: According to the levels of tumor dose, our cases were arbitrarily divided into three groups: the first group of 27 patients received irradiation with a dose of less than 5,000 rads, the second group of 56 ranging from 5,001 to 6,000 rads, and the third of group 44 of more than 6,001 rads. Among these three groups, there was no significant difference in regard to the location of the tumor. The result of analysis revealed that the higher tumor dose resulted in the longer survival time. Especially, the three year survival rate of the third group, 28 percent, was significantly better than that of the first and the second groups (Table VI). A similar result was obtained as to the nominal standard dose (NSD) in that irradiation with a dose of more than 1,701 rets resulted in the better survival rate than that with lower NSD (Table VII).

Table VA

SURVIVAL RATES ACCORDING TO TUMOR LOCATION

Location		Cerebrum			Midbrain and Brain Stem
		Right Hemisphere	Left Hemisphere	Bilateral Hemispheres	
No. of Cases		54	53	7	13
Average Tumor Dose		5,136 rads	5,480 rads	5,875 rads	4,686 rads
Standard Deviation		1,762	1,404	912	2,164
Percent Survival	6 mo.	85	72	57	46
	1 yr.	65	47	14	38
	2 yr.	48†	18†	14	0
	3 yr.	30*	14*	0	0
	4 yr.	20	9	0	0
	5 yr.	18	9	0	0

* $p < 0.05$ between figures.
† $p < 0.01$ between figures.

TABLE VB

SURVIVAL RATES ACCORDING TO TUMOR LOCATION IN CEREBRUM

Location		Right Frontal Lobe	Left Frontal Lobe	Right, Other Lobes	Left, Other Lobes
No. of Cases		23	18	31	35
Average Tumor Dose		4,897 rads	5,442 rads	5,360 rads	5,499 rads
Standard Deviation		2,047	1,457	1,469	1,396
Percent Survival	6 mo.	91	78	81	69
	1 yr.	70	45	61	49
	2 yr.	61†	6†	39	24
	3 yr.	48*	6*	16*	18
	4 yr.	38	6	6	11
	5 yr.	33	6	6	11

* $p < 0.05$ between figures.
† $p < 0.01$ between figures.
$p < 0.01$ between survival rate of right frontal and of other lobes as a group at 2 yr.
$p < 0.005$ between survival rate of right frontal and of other lobes as a group at 3 and 4 yr.
$p < 0.05$ between survival rate of right frontal and of other lobes as a group at 5 yr.

Field size: Among three groups of patients, irradiated through fields of less than 47 cm^2, 48 to 79 cm^2, or more than 80 cm^2, the highest survival rates up to three years were observed in the group irradiated through field size 48 to 79 cm^2 (Table VIII). However, there were no statistically significant differences of survival rates among the three groups. Three year survival rates were analyzed in relation to field size and tumor dose to assess the dose volume relationship (Table IX). Although an unfavorable prognosis was noted among the patients irradiated with a lower dose through a smaller field, there was no definite tendency that irradiation with a higher dose through a larger field resulted in a better survival rate at three years.

Long term survivors: Among the patients treated more than five years ago, six males and six females survived five years after radiation therapy. Six were alive for a period of 5.5 to 13 years, and of these, four have returned to normal and useful lives, being able to work as well as a normal person (Table X). Another six of five year survivors, however, died of recurrence of the tumor after a period ranging from 5.2 to seven years following radiation therapy. The tumor in these five year survivors was in the cerebral hemispheres in all twelve cases: right-sided in eight cases and left-sided in four cases. The tumor was located in the frontal lobe in seven of twelve. All

TABLE VI

SURVIVAL RATES ACCORDING TO TUMOR DOSE IN RADS

Tumor Dose		Under 5,000 rads	5,001 to 6,000 rads	Over 6,001 rads
No. of Cases		27	56	44
Percent Survival	6 mo.	56	79	80
	1 yr.	41	54	57
	2 yr.	26	27	34
	3 yr.	11	13*	28*
	4 yr.	11	11	15
	5 yr.	11	11	12

* $p < 0.05$ between figures.

Table VII

SURVIVAL RATES ACCORDING TO TUMOR DOSE IN RETS

N.S.D.		Under 1,400 rets	1,401 to 1,700 rets	Over 1,701 rets
No. of Cases		27	51	49
Percent Survival	6 mo.	60	77	80
	1 yr.	41	55	55
	2 yr.	26	25	35
	3 yr.	7*	17*	27*
	4 yr.	7	12	16
	5 yr.	7	12	13

N.S.D. = Nominal standard dose calculated by formula $D = N.S.D. \times N^{0.24} \times T^{0.11}$ 5.

* $p < 0.05$ between figures.

but one case were referred to our department for radiation therapy after subtotal or total resection of the tumor. Radiation dosage was more than 5,000 rads in all cases except for Case 12. Field size was less than 47 cm^2 in five cases, 48 to 79 cm^2 in five cases and more than 80 cm^2 in the remaining two.

DISCUSSION

The prognosis in the patients with glioblastoma is still extremely poor, despite advances in neurosurgery and radiation therapy. The survival rates in our series of astrocytomas Grade III and IV are somewhat higher than those reported by other authors (Table XI). However, it is impossible to compare the results of one series with those of another in terms of survival rates alone, because various biological characteristics of the tumor as well as treatment materially influence the prognosis.

Several authors state that the prognosis is closely related to age and sex of the patients. Roth and Elvidge[20] and Jones[10] report a relationship between young age and long survival, and state that patients under 35 years of age carry a more favorable prognosis than those over 36 years. Our results are similar to those reported by other authors, except for the poor prognosis among children under 15 years of age. The three year survival rate of the patients of 16 to 35 years was significantly higher than that of those over 36 years. The poor prognosis of children may be attributable to the pattern of tumor location which differs from that in adults. The tumors of children are frequently located in the brain stem and mid-brain, where the prognosis is extremely unfavorable (Table XII). Between the other two age groups, no significant difference

Table VIII

SURVIVAL RATES ACCORDING TO FIELD SIZE

Field Size		Under 47 cm^2	48 to 79 cm^2	Over 80 cm^2
No. of Cases		48	45	34
Average Tumor Dose		5,117 rads	5,464 rads	5,293 rads
Standard Deviation		1,719	1,417	1,727
Percent Survival	6 mo.	71	78	74
	1 yr.	48	58	50
	2 yr.	25	35	28
	3 yr.	13	28	16
	4 yr.	10	14	16
	5 yr.	10	12	16

TABLE IX

THREE YEAR SURVIVAL ACCORDING TO TUMOR DOSE AND FIELD SIZE

		Tumor Dose in rads			Total
		Under 5,000	5,001–6,000	Over 6,001	
Field Size	Under 47 cm²	0/14	2/16	4/18	6/48
	48–79 cm²	2/7	3/20	7/16	12/43
	Over 80 cm²	1/6	2/12	2/8	5/26
	Total	3/27	7/48	13/42	23/117

was noted in the distribution of tumor location. In regard to the influence of sex on the prognosis, Roth and Elvidge[20] report a slightly better prognosis for females than for males, however no such difference was noticed in our present series.

The grade of histological malignancy has been regarded as one of the important factors determining the prognosis of the patients with astrocytic gliomas.[10,27] However, conflicting results are reported in regard to the difference of survival time between patients with astrocytoma Grade III and those with Grade IV.[10,24,27] In addition, controversial opinions still continue as to the definition of glioblastomas. While astrocytomas Grade III and IV correspond to the glioblastoma multiforme according to

TABLE X

PATIENTS SURVIVED OVER FIVE YEARS AFTER RADIATION THERAPY

Case No.	Age and Sex	Location of Tumor	Surgical Removal	Tumor Dose		Size of Portal (cm×cm)	Quality of Survival
				In rads	In rets		
1	16 male	Left parieto-occipital	Subtotal	6,754	1,859	6×6	Excellent, living at 13 yr.
2	40 male	Right frontal	Subtotal	6,150	1,757	6×5	Partially disabled, living at 9 yr., 10 mo.
3	23 female	Right frontal	Lobectomy	5,920	1,683	8×7	Excellent, living at 9 yr.
4	57 female	Right frontal	Subtotal	6,010	1,568	9×8	Partially disabled, living at 8 yr.
5	26 female	Left temporal	Subtotal	6,100	1,744	10×8	Excellent, living at 6 yr., 4 mo.
6	39 male	Right frontal	Subtotal	6,000	1,722	10×8	Excellent, living at 5 yr., 6 mo.
7	25 male	Left temporal	Subtotal	5,100	1,498	8×6	Excellent until recurrence at 6 yr., died at 7 yr.
8	38 female	Right frontal	Lobectomy	5,900	1,720	6×6	Partially disabled, died at 6 yr., 7 mo.
9	7 female	Right parieto-occipital	Subtotal	5,000	1,450	9×7	Partially disabled, died at 5 yr., 10 mo.
10	32 male	Left frontal	Partial	5,120	1,631	6×6	Partially disabled, died at 5 yr., 8 mo.
11	27 male	Right temporal	Total	6,048	1,736	6×6	Partially disabled, died at 5 yr., 3 mo.
12	49 female	Right frontal	Lobectomy	2,547	1,049	8×6	Partially disabled, died at 5 yr., 3 mo.

Table XI

SURVIVAL RATES OF PATIENTS WITH GLIOBLASTOMA AFTER SURGICAL TREATMENT AND POSTOPERATIVE IRRADIATION

Author		No. of Cases	Percent Survival					
			6 mo.	1 yr.	2 yr.	3 yr.	4 yr.	5 yr.
Roth and Elvidge[20]	1960	144	78	35	18	10	8	6
Cocci[3]	1963	69		25		5		4
Bouchard[2]	1966	176		44		13		7
Schlienger[22]	1969	72	67	32	7	3	2	2
Lergé *et al.*[13]	1969	87		42	9	4	—	—
Jelsma and Bucy[9]	1969	40	80	40	18	—	—	—
Schütz *et al.*[23]	1971	67	63	24	9	4	4	—
Aristizibal and Caldwell[1]	1971	74	68	32	8	5	—	—
Our Series	1975	127	74	52	29	19	13	12

Kernohan and associates'[11] classification, Zülch[29] defines astrocytoma Grade IV as glioblastoma. The grade of an astrocytoma is usually determined on the basis of the most malignant part of the tumor. However, the histological findings of the biopsy material may not be representative, because most gliomas are pleomorphic and differ in appearance in various parts even within the tumor. It is not always feasible to differentiate strictly between astrocytoma Grade IV and Grade III. Therefore, patients with astrocytoma Grade III and IV were labelled glioblastoma together in our present series. Instead of histologic grading, survival rates were analyzed in terms of the duration of symptoms, which might be considered as indicative of the biological malignancy of the tumor. Stage and Stein[24] stated that the duration of symptoms bore an inverse relationship to the survival time of the patients. This was also the case in our series. A statistically significant difference of two years in survival was noted between those with duration over six months and those under six months. Further study revealed a close correlation between tumor location and the duration of symptoms. The patients with symptoms of longer duration were more frequently those with the tumor located in the right cerebral hemisphere (Table XIII). Since it is unreasonable to consider that the growth rate of a tumor differs significantly according to its intracranial location, the influence of symptom duration on

Table XII

RELATION BETWEEN TUMOR LOCATION AND AGE AT RADIATION THERAPY

Tumor Location	Age			Total
	Under 15 yr.	16–35 yr.	Over 36 yr.	
Right Cerebral Hemisphere	4	21	29	54
Left Cerebral Hemisphere	2	18	33	53
Bilateral Hemispheres	1	3	3	7
Midbrain and Brain Stem	8*	4	1	13
Total	15	46	66	127

* $p < 0.005$ for relative incidence.

Table XIII

RELATION BETWEEN TUMOR LOCATION AND SYMPTOM DURATION

Tumor Location	Duration of Symptoms			Total
	Under 3 mo.	3–6 mo.	Over 6 mo.	
Right Cerebral Hemisphere	16	15	23*	54
Left Cerebral Hemisphere	23	21	9	53
Bilateral Cerebral Hemispheres	2	3	2	7
Midbrain and Brain Stem	10*	1	2	13
Total	51	40	36	127

* $p < 0.01$ for relative incidence.

the prognosis may be regarded as secondary to the influence of tumor location, at least to some extent.

Intracranial location of the tumor has been reported to have a definite influence on the prognosis of the patients with glioblastoma.[8,9,20] A similar result was obtained in our series. Those with deep tumors carried a poor prognosis and none survived three years after treatment. Among patients whose tumors were located in a cerebral hemisphere, those with right-sided tumor had a more favorable prognosis than those with left-sided tumors. Furthermore, about one-third of those with a right frontal tumor survived more than five years after radiation therapy. Of twelve cases who survived more than five years, 6 cases have tumor in the right frontal and 1 in the left frontal lobe. In view of the rarity of a left-handed person in Japan, the right cerebral hemisphere may be regarded as minor hemisphere in most cases. Therefore, the difference of survival time among different tumor locations may be to some extent regarded as the result of the different degrees of surgical resection. The fact that all but one of the long term survivors received subtotal or total resection suggests the effect of extensive surgery.

The value of radiation therapy in the treatment of glioblastoma has been widely studied by many authors, of whom the majority state that radiation therapy can prolong the survival time of the patients in varying degrees.[6,14,20,21,25] However, most fail to elucidate the quantitative relation between radiation technique and survival. Since our series is not large, and we have no unirradiated controls, no definite conclusion as to the efficacy of irradiation can be drawn from our results. However, the survival rates in our series were markedly better than those of the unirradiated, which have been reported by other authors.[6,25] Moreover, the dose dependence of survival in our series may be regarded as evidence of the efficacy of radiation therapy.

Among the various factors of radiation therapy, dosage and field size will be discussed here on the basis of our results. A controversy continues as to the adequate dose of irradiation in the treatment of glioblastoma. Some authors[2,7,21] recommend a high tumor dose of more than 6,000 rads, while the others[1,24] consider that a high tumor dose does not result in longer survival time. Stage and Stein[24] state that the survival rates of those irradiated with a dose over 5,000 rads were considerably lower than those with a dose under 5,000 rads. Aristizibal and Caldwell[1] suggest that irradiation with doses ranging from 1,400 to 1,700 rets might result in the most favorable prognosis. Our series was irradiated with tumor doses of various levels up to 7,300 rads, however the highest survival rate was observed in the group irradiated with a dose of more than 6,001 rads or 1,701 rets. The survival rate at three years of the latter was significantly higher than that of those who received doses ranging from 5,001 to 6,000 rads. Since there was no significant difference in the survival rates at one and two years between both groups, it was unreasonable to consider that those irradiated with a smaller dose were under a specially unfavorable condition regarding the survival time. Therefore, it may be considered that a dose over 6,000 rads or 1,700 rets is necessary to prolong significantly the survival time of those with glioblastoma. Another important factor is the tolerance of normal brain tissue. Fortunately, there was no identified case of radiation necrosis in our series; however, we recommend a nominal standard dose not to exceed 2,000 rets, which corresponds to the upper line of the Lindgren's curve.[15]

A wide variety of opinions has been published concerning the adequate volume of irradiation. Concannon *et al.*[4] and Todd[26] recommend large volume irradiation, and state that there is no place for small or medium volume irradiation because of the infiltrative character of this tumor and the difficulty in accurate determination of the extent of the tumor. Kramer[12] advocates irradiation of the entire cranial contents, based on his study of tumor extent at autopsy. On the contrary, Ramsey and Brand[19] state that a significant increase in over-all survival time and tumor free period was found in the cases irradiated with a higher dose through limited fields. The results in our series fail to demonstrate definite dependence of survival time on field size (Tables VIII and IX). Since our plan of therapy used relatively limited fields in most cases, a large field was used only in case of an extensive tumor. In addition, there was a tendency to deliver a lower dose when irradiation was administered through a large field. Therefore, no definite conclusion on field size can be drawn from our results. However, the volume to be irradiated must be determined with due regard to the dose delivered, because the tolerance dose of the normal brain depends on the volume of irradiation. Todd[26] recommends a dose not to exceed 4,500 rads for a volume of 500 cc, 4,000 rads for 1,000 cc, and 3,750 rads for the whole brain, when irradiation is administered with 4 Mev x-ray over a period of three weeks. The nominal standard dose, calculated from these figures, corresponds to 1,700 rets for 500 cc, 1,500 rets for 1,000 cc, and 1,400 rets for the whole brain, respectively. Therefore, the volume of irradiation must be limited, when a high dose of radiation is necessary to control the tumor. In view of the limited radiosensitivity of glioblastomas, it is not advisable to irradiate an excessively large volume to avoid a geographic miss. In order to use irradiation effectively in the treatment of glioblastoma, it is necessary to determine more accurately the location and extent of the tumor and to deliver a high tumor dose of more than 6,000 rads to the limited volume according to the extent of the tumor.

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GROWTH ANALYSIS OF PULMONARY METASTASES FROM SALIVARY GLAND TUMORS*

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ABSTRACT:

Three cases of primary salivary gland tumors with lung metastasis are presented with extremely long survival (six, ten, and twelve years). The tumor doubling time was calculated and the growth rate of the pulmonary metastasis was found to be slow and erratic. A simplified table was devised, which permits rapid calculation of the tumor doubling time without the use of graphs. The presence of lung metastasis from some primary malignant salivary tumor is not necessarily an ominous sign: a long survival without symptoms is possible.

In patients with metastatic salivary gland malignancies, it is not unusual to note extraordinary examples of longevity. The behavior of this tumor is often attributed to slow growth, the propensity for local recurrence, and the frequent appearance of distant metastases—characteristic of all but the highly anaplastic muco-epidermoid and squamous cell varieties.

The lung is often the site of metastatic disease. Of 179 patients with malignant mucous and salivary tumors of all types presented by Rafla,[8] 23 percent had distant metastases and of these more than half were pulmonary. Adenoid cystic carcinoma, one type of tumor, metastasizes to the lungs in 20 to 37 percent of all cases.[5–7] Frazell[3] alludes to survivals greater than a decade in adenoid cystic carcinoma with pulmonary metastases, but does not cite specific cases. The longest reported survival of metastatic cylindroma was eight years;[12] other cases with survival of seven years,[7] six years,[9] and five years[8] appear in the literature. Moran *et al.*[7] emphasize the slow growth of cylindroma, having observed an average interval of 7.5 years between the clinical onset and the observation of the visceral metastases. Ryan[9] also reports the occurrence of chronic asymptomatic pulmonary metastases in one case, a clinical state which, he feels, deserves more emphasis in the literature.

The purpose of this paper is to add three case reports (two with cylindroma and one with malignant mixed-tumor of salivary origin) of patients with survivals twelve, ten, and six years, respectively. Analysis includes the application of the concept of doubling time and the introduction of another approach to the quantification of tumor doubling time.

BACKGROUND OF TUMOR DOUBLING TIME (T.D.T.)

In 1956, Collins *et al.*[2] introduced the concept of doubling time as a measure of cancer growth rate. Their hypothesis was based upon the assumption that cancer cells grow by division, which is essentially a "doubling" or exponential progression of the base 2. That is to say, that one cell gives rise to two, two to four, four to eight, etc. By plotting on a semi-log graph the serial measurements of metastatic pulmonary nodules against time, Collins and his co-workers noted a constant growth rate. Assuming that the initial cell was 10 microns in diameter, they point out that 20 doublings would produce a nodule of 1 mm diameter, another 10 doublings a nodule of 1 cm diameter, and another 15 doublings a tumor equal to half the weight of a 70 kilogram man.[2] Note that the majority of growth occurs well below the threshold of detectability, and that the so-called "early" lesion noted on chest roentgenogram is in actuality a late manifestation of the disease.

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In the literature, the application of the doubling time concept has usually been expressed by graphic analysis as per Collins and associates' original paper. Our initial approach to quantification of tumor growth involved the construction of a table relating roentgenographic diameter of a nodule to its volume. By noting the change in volume within a specified time interval, computation of doubling time was then possible. Further refinement of the table was then attempted by more detailed analysis of the change in diameter when the volume of a hypothetical nodule was gradually increased. This table (Table 1) related changing diameter (ΔD) with the degree of tumor doubling. Doubling time was determined by dividing the degree of tumor doubling (dbl) by the time elapsed. Use of this table permitted rapid calculation of doubling time, without the use of log tables and slide rule. Furthermore, this obviated the construction of graphs, an unwieldy process when tumor growth covers varying time intervals and extended time periods.

Examination of the approximation formula of Schwartz[10] revealed that in actuality this table was essentially a tabular representation of a hypothetical range of values satisfying the equation:

$$\text{dbl} = 10 \times \log \frac{D_t}{D_0}$$

where D_t = diameter at time t, D_0 = initial diameter, and dbl = degree of tumor doubling.

METHOD

Periodic chest roentgenograms were analyzed for nodule size with a mean of three measured diameters recorded. Care to insure reproducibility included maintenance of standard 6 foot posteroanterior chest films. Nodules of less than one centimeter as a rule were ill-defined, and were excluded from measurements because variations of 1 millimeter introduced a significant error. The ratio of diameters observed, D_t/D_0, or ΔD, was calculated. (D_0 = initial diameter; D_t = diameter at time t.) Then, the number of tumor doublings (dbl) was obtained from Table 1 by inspection. Tumor doubling time was determined by the division of the degree of tumor doubling (dbl) by the time elapsed.

Hypothetical Case:

Size of one initial nodule = 1 cm

Size of nodule 365 days later = 2 cm

$$\Delta D = \frac{2}{1} = 2$$

From chart: 2 ΔD = 3.01 dbl

365 ÷ 3.01 = 121 days doubling time

REPORT OF CASES

CASE 1. H.S. In 1954, this 32 year old male presented himself at the Albert Einstein Medical Center for postoperative radiation therapy to para-aortic and pelvic lymph nodes after orchiectomy for a seminoma of the right testicle. Past history included resection of a malignant mixed tumor of the parotid gland in 1948. Three months after completion of radiation therapy and six months after orchiectomy, a chest roentgenogram revealed two nodules in the right lung. These nodules disappeared completely in three months, without treatment (evidence of possible spontaneous regression of metastatic testicular cancer).[1]

Local recurrences of the parotid tumor were resected in 1955, 1956, 1957, 1964, 1969, 1971 and 1972. Multiple lung metastases were first noted in 1967, but in retrospect a nodule in the right cardiophrenic sulcus had been present as early as 1964. Thoracotomy in 1967 established the nodules to be malignant mixed tumor and not seminoma. No treatment was directed to the pulmonary lesions, which have slowly increased in size. Bone metastases to the skull were noted in 1969, also slowly progressive. Despite his advanced disease (Fig. 1), the patient

Table I

THE CALCULATED DOUBLES OF THE TUMOR ACCORDING TO THE CHANGE IN DIAMETER (ΔD)

ΔD	DBL	ΔD	DBL	ΔD	DBL	ΔD	DBL	ΔD	DBL	ΔD	DBL
1.00	0.00	1.30	1.14	2.0	3.01	5.0	7.00	8.0	9.03	11.0	10.41
1.01	0.04	1.32	1.21	2.1	3.22	5.1	7.08	8.1	9.09	11.1	10.45
1.02	0.09	1.34	1.27	2.2	3.42	5.2	7.16	8.2	9.14	11.2	10.49
1.03	0.13	1.36	1.34	2.3	3.62	5.3	7.24	8.3	9.20	11.3	10.53
1.04	0.17	1.38	1.40	2.4	3.80	5.4	7.32	8.4	9.24	11.4	10.57
1.05	0.21	1.40	1.46	2.5	3.98	5.5	7.40	8.5	9.29	11.5	10.61
1.06	0.26	1.42	1.52	2.6	4.15	5.6	7.48	8.6	9.35	11.6	10.65
1.07	0.29	1.44	1.58	2.7	4.31	5.7	7.56	8.7	9.40	11.7	10.68
1.08	0.33	1.46	1.64	2.8	4.47	5.8	7.63	8.8	9.45	11.8	10.72
1.09	0.38	1.48	1.70	2.9	4.62	5.9	7.71	8.9	9.49	11.9	10.76
1.10	0.41	1.50	1.76	3.0	4.77	6.0	7.78	9.0	9.54	12.0	10.79
1.11	0.46	1.52	1.82	3.1	4.91	6.1	7.85	9.1	9.59	12.1	10.83
1.12	0.49	1.54	1.88	3.2	5.05	6.2	7.92	9.2	9.64	12.2	10.86
1.13	0.53	1.56	1.93	3.3	5.19	6.3	7.99	9.3	9.69	12.3	10.90
1.14	0.57	1.58	1.99	3.4	5.32	6.4	8.06	9.4	9.73	12.4	10.93
1.15	0.61	1.60	2.04	3.5	5.44	6.5	8.13	9.5	9.78	12.5	10.97
1.16	0.65	1.62	2.10	3.6	5.56	6.6	8.20	9.6	9.82	12.6	11.00
1.17	0.68	1.64	2.15	3.7	5.68	6.7	8.26	9.7	9.87	12.7	11.04
1.18	0.72	1.66	2.20	3.8	5.80	6.8	8.33	9.8	9.91	12.8	11.07
1.19	0.76	1.68	2.25	3.9	5.91	6.9	8.39	9.9	9.96	12.9	11.11
1.20	0.79	1.70	2.30	4.0	6.02	7.0	8.45	10.0	10.0	13.0	11.14
1.21	0.83	1.72	2.36	4.1	6.13	7.1	8.51	10.1	10.04		
1.22	0.86	1.74	2.41	4.2	6.23	7.2	8.57	10.2	10.08		
1.23	0.90	1.76	2.46	4.3	6.34	7.3	8.63	10.3	10.13		
1.24	0.93	1.78	2.50	4.4	6.44	7.4	8.69	10.4	10.17		
1.25	0.97	1.80	2.55	4.5	6.53	7.5	8.75	10.5	10.21		
1.26	1.00	1.83	2.63	4.6	6.63	7.6	8.81	10.6	10.25		
1.27	1.04	1.86	2.70	4.7	6.72	7.7	8.87	10.7	10.29		
1.28	1.07	1.90	2.79	4.8	6.81	7.8	8.92	10.8	10.33		
1.29	1.11	1.93	2.86	4.9	6.90	7.9	8.98	10.9	10.37		
		1.96	2.92								

ΔD = change of diameter.
DBL = doubles.

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is surprisingly well, gainfully employed, and free of pulmonary symptoms referable to his lungs.

Comment. Calculation of tumor doubling time of two nodules demonstrates slow but erratic growth, varying from 256 to 1,380 days (Table II). Onset of lung metastases was 16 years after the initial diagnosis. Extrapolation to time of the first metastasis, based upon doubling time of the longest and shortest intervals, revealed the first 10 micron cell implanted between 23.6 and 96 years previously! Therefore, this patient was younger than 13.4 years old when the parotid gland metastasis began to grow—clearly impossible.

Case II. E.S. In 1967, this 60 year old white female presented with right facial nerve paresis, right parotid enlargement, and a four year history of pain in the right temporomandibular joint. The parotidectomy specimen revealed an "adenoid cystic carcinoma." Lung metastasis occurred one year after postoperative irradiation treatment. Since that time, the metastases have increased in size and number (Fig. 2). Presently, six years after lung metastasis was noted, the patient is living and complains only of mild dyspnea on exertion.

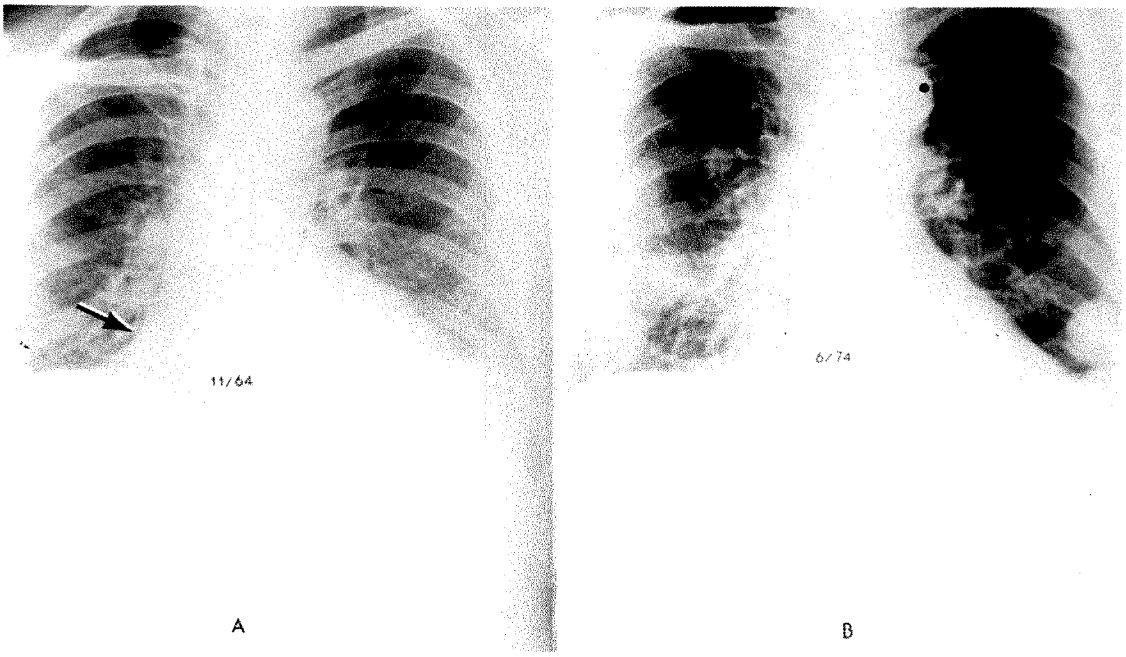

FIG. 1. Case I. (*A*) Note lesion at right cardiophrenic angle which was removed in 1967 and reported as metastatic seminoma. (*B*) Most recent roentgenogram, patient asymptomatic.

CASE III. P.P. In 1966, this 77 year old white male presented with a history of "basal cell carcinoma" of the chin diagnosed in 1944. The lesion recurred repeatedly, necessitating radical excisions and bone grafts of the mandible on two occasions. The lesion was reinterpreted histologically in 1954 as adenocarcinoma of salivary origin, and cylindroma, on recurrences in 1959 and 1966. Chest roentgenograms in 1959 revealed bilateral metastases, which slowly increased in size over the years. Calculation of tumor doubling time was not possible because of the ill defined nature of the metastasis prohibiting measurements. The patient remained asymptomatic with no pulmonary complaints, despite the advanced state of the pulmonary metastasis. In 1971, he committed suicide at age 83, twelve years after discovery of lung

TABLE II

CALCULATED TUMOR DOUBLING TIME OF NODULES ABC: CASE I

Date	Nodule A		Nodule B		Nodule C	
	Diameter (cm)	TDT* (days)	Diameter (cm)	TDT (days)	Diameter (cm)	TDT (days)
11-10-64	3.2	—	Neg.	—	Neg.	—
11-14-67	5.7	440	1.8	—	2.0	—
3-13-69	N.M.†	—	2.1	748	2.5	500
9-23-69	N.M.	—	2.6	254	2.8	388
4-27-71	N.M.	—	3.0	932	3.2	1,000
5-23-72	N.M.	—	3.2	1,380	3.5	990
6-19-73	N.M.	—	3.5	1,010	3.8	1,088
12-11-73	N.M.	—	3.8	539	4.1	570

* TDT = tumor doubling time.
† N.M. = not measurable.

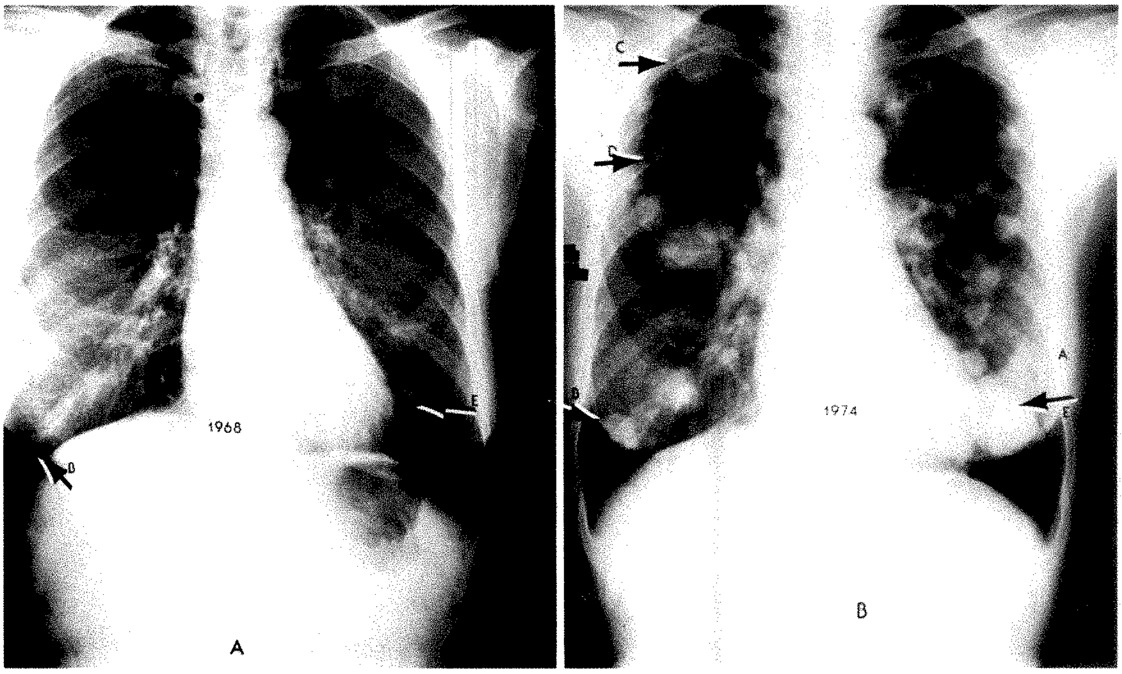

Fig. 2. Case ii. (*A*) Metastasis first noted in 1968. (*B*) Most recent film, patient has slight dyspnea on exertion and is not receiving any systemic therapy.

metastasis. A chest roentgenogram demonstrating the advanced disease is shown in Figure 3.

RESULTS

Doubling time data are presented in Tables ii and iii. As expected, all tumor doubling times are prolonged, but growth is not accurately predictable. The data of Case i reveal that during the 26 month interval of April 27, 1971 to June 19, 1973, growth was more or less uniform with a tumor-doubling time range of 932–1,088 days. However, prior to that interval, the smaller nodules had faster tumor doubling times with a range of 254–748 days. It was thought that these data supported the concept of a slow terminal growth phase. However, the last observation contradicted this principle since tumor doubling time again fell in a range of faster growth (270 days).

Comparison of nodules B, C and E of Case ii (Fig. 2) revealed that during the 16 month interval of February 29, 1972 to July 31, 1973, the largest nodule (E) had predictable growth (tumor doubling time = 297–298 days) while C slowed (289–442 days), and B accelerated (333–269 days). This independent variation suggests that local factors, such as blood supply, oxygenation, and necrosis, may provide significant influence on tumor growth.

DISCUSSION

In the past, when pulmonary metastasis from salivary gland tumors was discovered, the prognosis became extremely poor. But the literature does contain references to long survivals. Two of the cases presented represent the longest reported survivals. Case iii died by suicide and not from his lung metastasis, a ten year survival. Case i represents a ten year survival, and is still alive and asymptomatic. Based upon the "lethal boundary" proposed by Spratt and Spratt,[11] he should survive at least another eight doubles. If future tumor doubling time is estimated at 500–1,000 days, this would represent an additional survival of

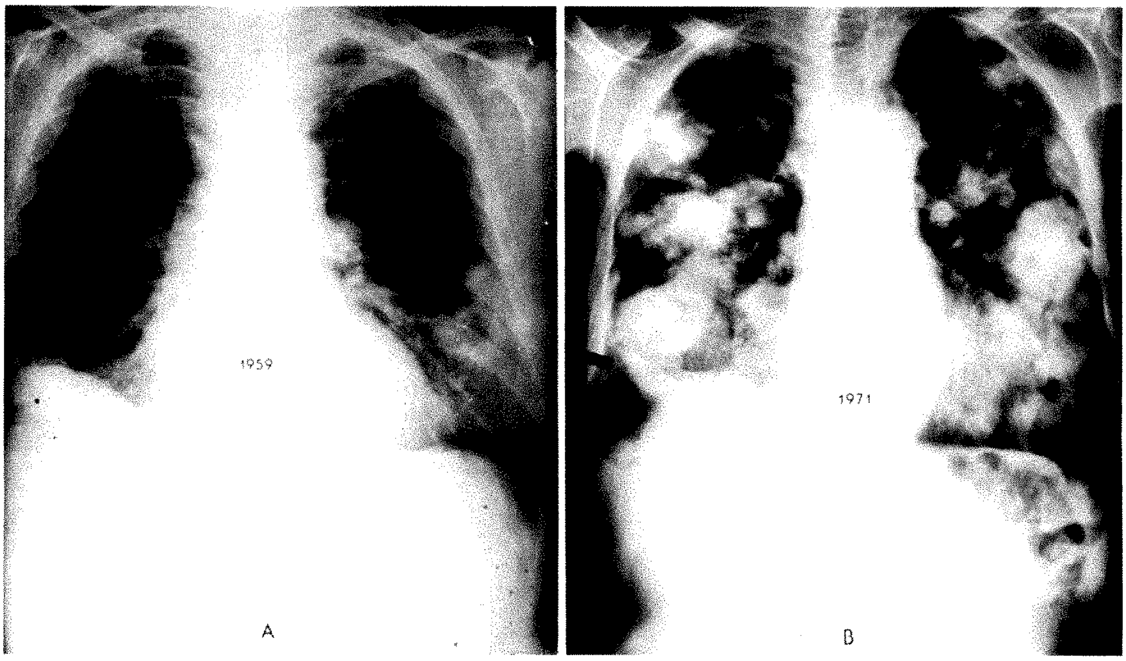

FIG. 3. Case III. (*A*) Metastasis first noted 14 years after original surgery. (*B*) Last chest roentgenogram, patient still asymptomatic and not receiving any systemic therapy.

eleven to 22 years. Likewise, Case II has an estimated 6.5–8.5 years additional survival, based upon estimated future tumor doubling times of 300–400 days for nodule E (the largest).

Over-all, the analysis of growth of lung metastasis in two cases has produced a wide range of slow growth which is erratic, and does not conform to exact exponential predictions. The noted variation of tumor doubling time of the same nodules after successive observations, and of different nodules during the same time interval, emphasizes the error in characterizing the natural history of a tumor based upon limited observation. Similarly, in an analysis of his own cases and those of others, Weiss[13] also notes lack of constancy of growth of bronchogenic carcinoma when untreated cases have an extended period of observation.

Joseph *et al.*[4] have demonstrated considerably improved survivals after aggressive surgical resection of solitary and multiple pulmonary metastases whose tumor doubling times were greater than 40 days. However, of the eleven patients in their category, only two had very slow tumor doubling times (both 360 days). Follow-up of four and 28 months of these cases is not of sufficient duration to confirm that the surgery contributed to longevity. Certainly, the patients described in this report would have represented erroneously favorable statistics had they been subjected to excision of their metastases. Furthermore, the diffuse bilaterality of the lesions would lead one to surmise that had they been resected, pulmonary function would have been compromised considerably. Therefore, a qualified category is needed in which the contribution of aggressive surgery to longevity is unproved when tumor doubling time is extremely long.

Doubling time remains the best method available for measuring tumor growth. The simplified tabular approach to its calculation presented in this report should permit calculation of tumor doubling time as well as standardization of the application of this principle. The practicing clinician need no longer make crude estimations

Table III

CALCULATED TUMOR DOUBLING TIME OF NODULES BCDE: CASE II

Date	Nodule B		Nodule C		Nodule D		Nodule E	
	Diameter (mm)	TDT* (days)	Diameter (mm)	TDT (days)	Diameter (mm)	TDT (days)	Diameter (mm)	TDT (days)
5-29-69	N.M.†	—	N.M.	—	N.M.	—	12.2	—
11-25-69	9.2	—	9.7	—	N.M.	—	13.2	518
2-29-72	16.3	331	18.7	289	11.8	—	25.0	297
7-31-73	25.4	269	24.5	442	17.1	320	37.3	298
1- 8-74	N.M.	—	26.0	6.4	18.5	450	41.0	388
4- 2-74	N.M.	—	27.0	600	19.5	407	43.5	360

* TDT = tumor doubling time.

† N.M. = not measurable.

of the growth characteristics of chest nodules. Thus, the body of published works relating to tumor doubling time can be more universally applied, deeply analyzed, and cogently expanded.

SUMMARY

Three cases of salivary gland tumors, metastatic to lung, are reported with long survivals of six, ten, and twelve years. Emphasized is the slow growth of lung metastasis from some primary salivary gland tumors, without treatment, and the lack of associated pulmonary symptoms. Application of the doubling time concept reveals that while growth is slow, it is not constant and may be dominated by local influences. A simplified tabular approach to quantitation of doubling time is presented.

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CONCEPTS FOR TREATMENT OF MICROMETASTASES DEVELOPED IN MURINE SYSTEMS*

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ABSTRACT:

Small tumor cell foci, whether left *in situ* during primary surgical excision or escaping lethal radiation damage, as well as distant metastases, are the primary reason for treatment failure in man and are the proper targets for the chemotherapist and immunotherapist. Since cure probably requires reduction of the total body burden of tumor cells to very small numbers (possibly to less than one cell), and since first-order kinetics of tumor cell kill by drugs appears to be a natural law in cancer chemotherapy, drug treatment should be started as soon as possible after likely noncurative primary treatment with surgery or radiation.

Current knowledge of tumor cell population growth kinetics indicates that the growth fraction (viable tumor cells undergoing active cell replication) is inversely related to population size. Tumor cells in micrometastases should, therefore, be more sensitive to anticancer drugs active against anabolizing cells than are tumor cells in the larger, grossly apparent primary tumor from which they were derived. This indicates the probability that micrometastases will be effectively responsive to more drugs than is the primary and clinically apparent tumor from which they came.

Studies with at least four metastatic and uniformly fatal murine solid tumors (lung, breast, colon, and melanoma) have demonstrated significantly improved cure rates with drug treatment following surgical removal of the grossly apparent primary tumor than can be obtained with either surgery or drug treatment when used alone. Further, both disease staging and drug dosage have been shown to influence cure rates of combined-modality treatment.

With several mouse tumors, a significantly smaller number of viable tumor cells can establish lethal tumors in the presence of radiation-inactivated tumor cells than in their absence. This suggests that small numbers of residual viable tumor cells in radiation-treated tumor sites may be a greater threat to clinical cure than smaller tumor cell populations remaining *in situ* after surgery.

SIGNIFICANT increases in cure rates of human tumors continue to be obtained with both surgical and radiation treatment. This progress will doubtless continue, but even the most partisan surgeons and radiologists do not predict ultimate total control, by their medical subdiscipline, of tumors which have metastasized when first detected. The great promise of and need for cancer chemotherapy and immunotherapy is to kill viable* tumor cells in metastatic foci which are not vulnerable to surgical removal or radiation kill because of multiple, diverse, and often unrecognized anatomic sites. Of the more than 665,000 people in the United States who will develop clinically recognized cancer this

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* For this discussion, a viable tumor cell is defined as one capable of maintaining uncontrolled cell division until the lethal number is reached.

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year, more than 50 percent will have metastatic disease at the time of diagnosis, or at least will have a high risk of tumor recurrence following currently optimal surgical, roentgenological, or combined treatment.[3] These metastatic tumor foci are the proper target for the chemotherapist and the immunotherapist.

That a number of widely disseminated human tumors are curable by, or show useful therapeutic response to, drug treatment is an objective reality.[3] How do we all (surgeons, radiologists, chemotherapists, and immunotherapists) extend our current success?

REQUIREMENTS FOR CANCER "CURE"

By "cure" I mean removal (surgical) or destruction (kill by radiation or drugs) of a large enough fraction of the viable tumor cell population so that those tumor cells remaining after treatment can never reestablish the clinically recognized disease. That a single cancer cell can establish fatal disease in several mammalian species with a number of different neoplastic cell types has been repeatedly demonstrated by laboratory workers around the world (Table 1). Also, production of specific immunoglobulins by some myelomas of man and animals, and immunologic specificity commonly observed in tumors induced by chemical oncogens, indicate tumor origin from a single cell.[1] These observations suggest that total tumor cell removal or kill by surgical, radiation, drug, immunologic, or combined treatment is required for cure.

Table I

LETHAL TUMORS FROM IMPLANT OF ONE MICROMANIPULATOR-ISOLATED TUMOR CELL

Tumor	Host	Reference
Leukemias and Plasma Cell Tumors		
AKF5 Leukemia and and S2 Leukemia	Mouse	8
L1210 Leukemia	Mouse	40
L1210 Leukemia resistant to 6-Mercaptopurine, 6-Methyl mercaptopurine, 8-Azaguanine, or Methyl-GAG	Mouse	29
Plasmacytoma No. 1	Hamster	29
Solid Tumors		
Yoshida Sarcoma	Rat	16
Jensen Sarcoma	Rat	31
Sarcoma 37	Mouse	32
Hepatoma AH-66F, AH-272, and AH-130	Rat	46
Walker Carcinosarcoma 256	Rat	29
Sarcoma 180	Mouse	

If surgical, radiation, or combined therapy removes or kills all clinically visible or detectable tumor foci, but unrecognized metastases remain, what is the likely total body burden of viable cells? The likely tumor cell populations of micrometastases are shown in Table II.[30] These estimates are based on the indicated probability that each gram of tumor may contain as many as 10^9 cells.[3,40] A single metastatic focus, 1 mm in diameter, may contain 10^5–10^6 tumor cells, and this number will range downward to one cell with progressively smaller metastases. The number and size of these micrometastases will determine the likely tumor cell kill requirements for cure. It is highly variable, but in many cases the total tumor cell population in unrecognized metastases may be very large and formidable, especially if reduction to small numbers (perhaps to less than one) may be required for cure.

Table II

APPROXIMATE NUMBER OF TUMOR CELLS IN SMALL METASTATIC FOCI

Diameter of Metastasis		Approximate Number of Tumor Cells Assuming Diameter of Tumor Cell to Be:	
mm	microns	10 microns	15 microns
1/4	250	1.6×10^4	4.6×10^3
1/2	500	1.3×10^5	3.7×10^4
3/4	750	4.2×10^5	1.3×10^5
1	1,000	1.0×10^6	3.0×10^5
2	2,000	8.0×10^6	2.4×10^6
5	5,000	1.3×10^8	3.7×10^7
10	10,000	1.0×10^9	3.0×10^8

DRUG TREATMENT

This subject cannot be treated in a simple manner. Proper selection and application of effective anticancer drugs are changing rapidly as new drugs and improved procedures for their application are developed. Drug selection and application should properly be determined by a well-trained and knowledgeable medical oncologist. Two cardinal principles of anticancer drug therapy should be cited, however, because they are basic and, if not confusing, often poorly understood.

Kinetics of Tumor Cell Kill by Effective Anticancer Drugs. First-order kinetics of drug kill of tumor cells appears to be a natural law in cancer chemotherapy. Simply stated, there is a constant percentage tumor cell kill, irrespective of population size, as long as the dose of drug is constant and effective, and the tumor cell population is metabolically homogeneous.[30,40,41] This principle seems illogical to many biologists, but not to bacteriologists and radiologists. They have long recognized first-order kinetics of germicidal cell kill of bacteria *in vitro* and first-order kinetics of cell kill by constant doses of radiation. If drug kill of tumor cells *in vivo* is due to chemical reactions, then that these reactions should follow the laws of physical chemistry should be anticipated and predictably demonstrable, as they are.[43]

Tumor Cell Population Kinetics. It has been repeatedly shown that the time duration of the division cycle (T_C) of the tumor cells of a number of different murine tumors (carcinomas, melanomas, and leukemias) is directly related to tumor mass—the larger the tumor cell population, the longer the T_C.[14,20,34–36,42,45] Reduction of total body burden of tumor cells by effective but noncurative drug therapy has also been shown to shorten the T_C in acute lymphoblastic leukemia[18] and ovarian cancer in man.[33] Also, the T_C of cells in micrometastases of Lewis lung carcinoma in mice is significantly shorter than that of cells in the primary tumor (in the same host) which shed the tumor cells to the metastases.[36] Reduction in total body burden of tumor cells has been shown to decrease the tumor mass doubling time with sarcoma 180 and adenocarcinoma 755 in mice.[28] This indicates that the fraction of the total viable tumor cell population in actual cell division increases as the tumor burden is decreased. This should forecast increased cell kill by those drugs limited in cytotoxic activity to dividing tumor cells as the tumor burden is reduced, and this has been objectively demonstrated for arabinosylcytosine.[13,30]

These two cardinal principles clearly indicate that (a) chemotherapy as an adjuvant to either surgical or roentgenologic treatment of cancer should be started as soon as possible after the primary treatment, and (b) drug response of the clinically apparent tumor masses may not predict the qualitative or quantitative sensitivity of tumor cells in micrometastases, especially to those anticancer drugs limited in cytotoxic activity to anabolizing tumor cells.

The selective kill potential for tumor cells of our best currently available anticancer drugs is, with very few exceptions (either drug or tumor), well below the likely total tumor burden in most patients at clinical presentation with most tumors. Additionally, it is now well established that with experimental tumors in animals, qualitative drug sensitivity is increasingly more evident as total body burden of tumor cells is decreased.[38,39] Clinically undetectable and often multiple and diffuse micrometastases should be vulnerable to chemotherapy.

Indications for Adjuvant Chemotherapy

A. *Population Kinetics of Viable Tumor Cells Surviving Noncurative Drug Treatment.*

Wilcox and co-workers[44] developed the concept that regression and regrowth of solid tumors treated with effective but noncurative therapy (drug treatment or radiation) could be considered a constantly varying summation of two factors: (1) lysis and resorption of killed tumor cells; and (2) continuing multiplication of tumor cells surviving therapy. This concept is illustrated in Figure 1. The solid line is the observed tumor mass curve following effective but noncurative drug treatment (about 90 percent tumor regression). Assuming that the tumor cells surviving therapy continue to divide at the same rate after treatment as they did before (they probably divide more rapidly, as discussed above), and that the cells killed by treatment are resorbed at some approximately constant rate, one can conclude that the viable cells surviving therapy would be much fewer than would be estimated from observations of tumor mass after therapy. The nadir of tumor mass would be at a time when very significant regrowth of tumor cells surviving treatment had occurred. This concept was objectively tested[12,37] (Fig. 2). A sensitive bioassay procedure for viable cells in a transplantable plasmacytoma (Pla. 1) in hamsters has been developed.

Hamsters were implanted subcutaneously with Pla. 1. About five days postimplant, the growing tumors were palpable (about 60 mg) and by day eight they were about 800 mg in size and continued to grow (Line A—untreated controls). After treatment of animals on day eight with a single noncurative and nontoxic but effective dose of cyclophosphamide (Line B), the tumor mass remained essentially static for a few days and then regressed, reaching a nadir in five to seven days after treatment. The tumor then resumed growth at a rate approximating its rate of increase prior to drug treatment. Bioassay of the viable tumor cells before drug treatment and during regression and regrowth (Line C) indicated that the viable tumor cells per unit mass of the tumor decreased by 4–5 orders of ten between four and 24 hours after treatment, and the surviving tumor cells repopulated the tumor at a rapid rate. Similar studies on tumor mass and bioassay of viable tumor cells in large (about 500 mg) sarcoma 180 and adenocarcinoma 755 tumors in mice have yielded essentially the same results as those shown here with Pla. 1.[27]

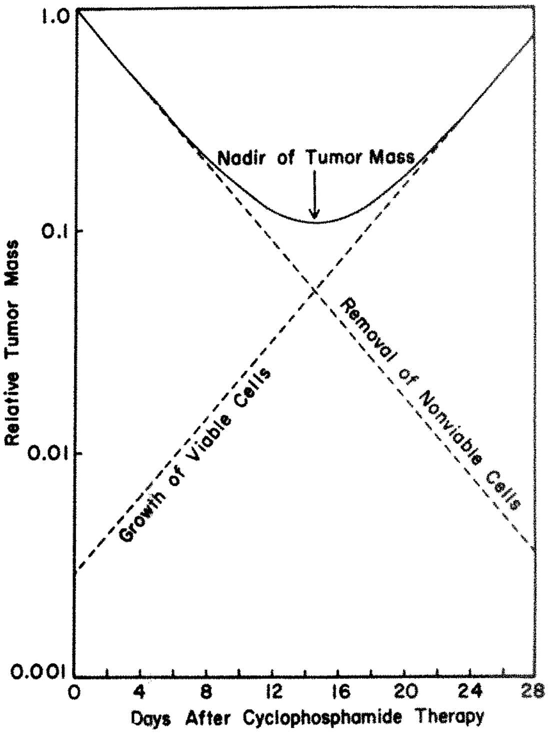

FIG. 1. Theoretical regression and regrowth of a solid tumor following effective but noncurative treatment. Tumor mass is an integration of dividing viable cells surviving treatment and resorbing cells killed by the treatment. The solid line is the observed tumor mass.

Two very important concepts may be derived from these common observations: (1) tumor cell kill by drugs (and likely also by radiation) may be significantly underestimated from tumor mass observations following effective but noncurative treatment; and (2) the optimal time for adjuvant or sequential drug therapy following any noncurative primary treatment is probably as soon after such treatment as possible, and not at the nadir or during obvious regrowth of the solid tumor.

B. *Surgical Adjuvant Chemotherapy.*

All of the concepts presented above support the indication for early postsurgical or postradiation adjuvant chemotherapy to kill tumor cells in metastases, those remaining in or around the primary site, or all. Recently reported encouraging results with

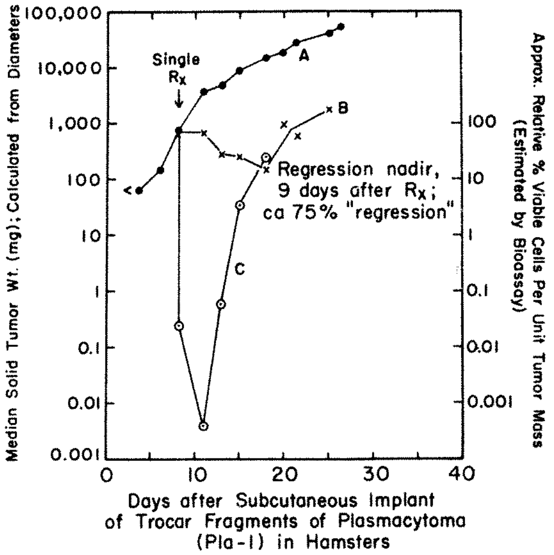

Fig. 2. Relationship between behavior of solid tumor mass and tumor cell viability of Pla. 1 treated with a single dose of cyclophosphamide. (A) Untreated control tumors. (B) Tumor mass after treatment with a single dose of cyclophosphamide (25 mg/kg) on day eight postimplant; the nadir is on day 18, nine days after treatment; about 75 percent tumor regression occurred. (C) Approximate relative percent of viable tumor cells per unit of tumor mass as determined by *in vivo* bioassay; about 99.999 percent tumor cell kill was obtained; the nadir of viable cells occurred shortly after treatment.

early postsurgical adjuvant chemotherapy, in breast tumor patients[6] and osteogenic sarcoma patients[2,17] with a high risk of metastatic tumor recurrence, make similar studies with these and other tumors with a high risk of metastatic spread at time of surgery clearly indicated. There are several metastatic solid tumors of mice with which significant surgical adjuvant drug cure rates can be obtained when surgery is delayed until curative surgical failure rates are high.

Figures 3–6 present data illustrating curative surgical adjuvant chemotherapy with four metastasizing solid tumors of mice which are considered to be very unresponsive to chemotherapy.

Lewis Lung Carcinoma (Fig. 3). By about seven days after subcutaneous implantation of this tumor in mice it has metastasized to the lungs, and surgical removal fails to provide any cures or to increase host survival time over that of untreated controls.[22]

Curative surgical adjuvant chemotherapy with cyclophosphamide (CPA)[15,19,22] and other drugs[22] has been reported, and illustrative data from Southern Research Institute are shown in Figure 3. Surgical excision of the primary tumor on day twelve postimplant or treatment with CPA on days 13 and 20 postimplant failed either to cure or to extend life span significantly; either modality, when used alone, was essentially ineffective. However, surgical removal of the primary tumor on day twelve and CPA treatment on days 13 and 20 resulted in a 50 percent cure rate and significant increase in life span of animals ultimately dying of tumor.

B16 Melanoma (Fig. 4, *A* and *B*).[11] This tumor had an 80 to 90 percent curative surgical failure rate associated with metastatic spread by day twelve to day 15 postimplant. Treatment with *N*-(2-chloroethyl)-*N'*-(*trans*-4-methylcyclohexyl)-*N*-nitrosourea (MeCCNU) without surgical removal of the primary tumor was not curative and increased median life span of treated mice only to a limited degree. Surgical adjuvant chemotherapy increased the cure rate from 20 to 70 percent when given on day 13,

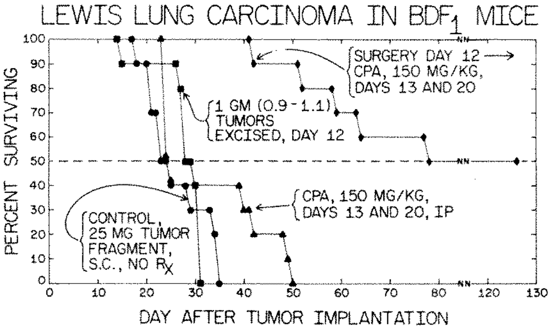

Fig. 3. Curative surgical adjuvant chemotherapy of Lewis lung carcinoma with surgical removal of the primary tumor (no cures); treatment with cyclophosphamide (CPA) on days one and eight after surgery (no cures); surgery followed by CPA (50 percent cured).

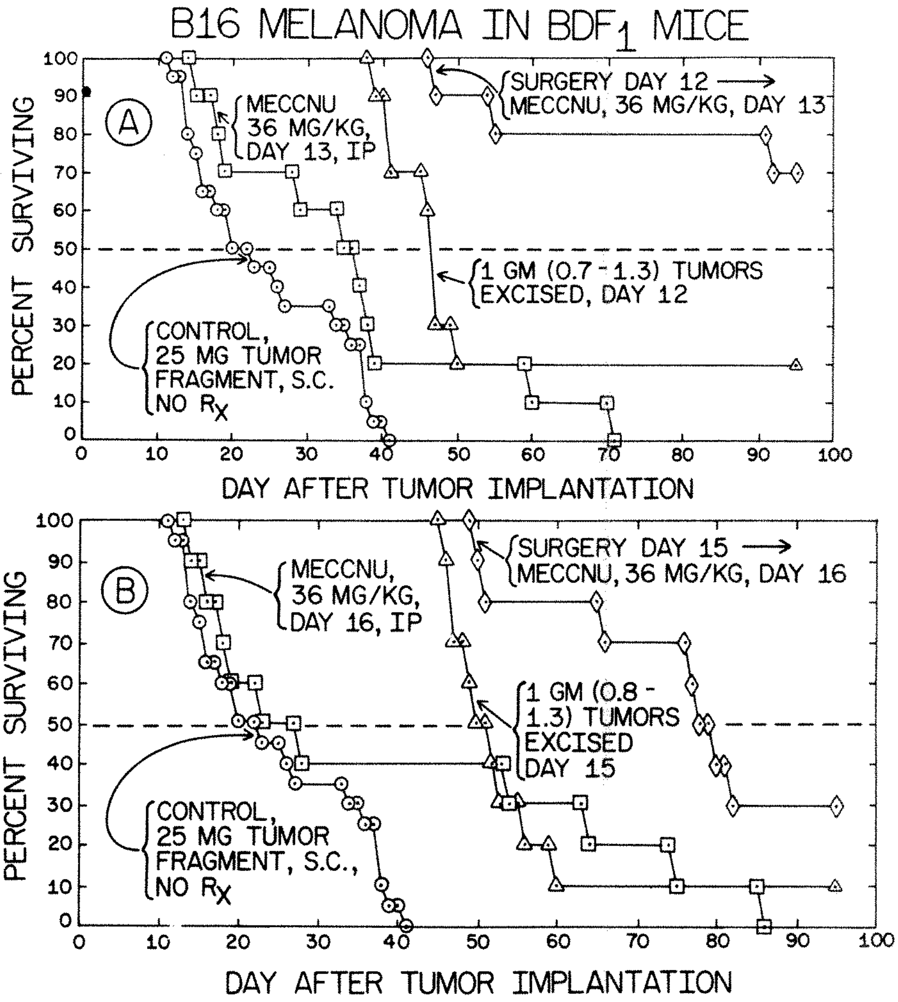

Fig. 4. Surgical adjuvant chemotherapy of B16 melanoma. Influence of tumor staging (body burden of tumor cells) on cure rates. (*A*) Surgery on day twelve postimplant (20 percent cured) followed by single-dose treatment with MeCCNU 24 hr later. MeCCNU treatment without surgery was not curative. Surgery followed by MeCCNU raised cure rate to 70 percent. (*B*) Same as *A*, except start of treatment was delayed to day 15 postimplant. Surgical cure rate reduced to ten percent and surgical adjuvant chemotherapy cure rate reduced to 30 percent.

24 hours after surgery on day twelve (Fig. 4*A*). When surgery was delayed to day 15 postimplant, adjuvant chemotherapy increased the cure rate only from ten to 30 percent, but did markedly increase the life span over that with surgery alone in those dying animals (Fig. 4*B*). These data clearly indicate the importance of disease staging (body burden of tumor cells) to curative surgical adjuvant chemotherapy.

C3H Mammary Adenocarcinoma (Fig. 5*A–C*).[10] This tumor had a curative surgical failure rate of 70 percent to more than 90 percent on days eleven to 14 postimplant, and 100 percent curative failure with drug treatment with *N,N'*-bis(2-chloroethyl)-*N*-nitrosourea (BCNU) plus CPA or *cis*-4-[[[(2-chloroethyl)nitrosoamino]carbomyl]-amino]-cyclohexanecarboxylic acid (CCCNU-*cis*) plus CPA on days 15 to 18 postimplant. However, BCNU plus CPA four days after surgical removal of the primary tumor on day eleven increased the cure rate from 20 percent with surgery alone to 100

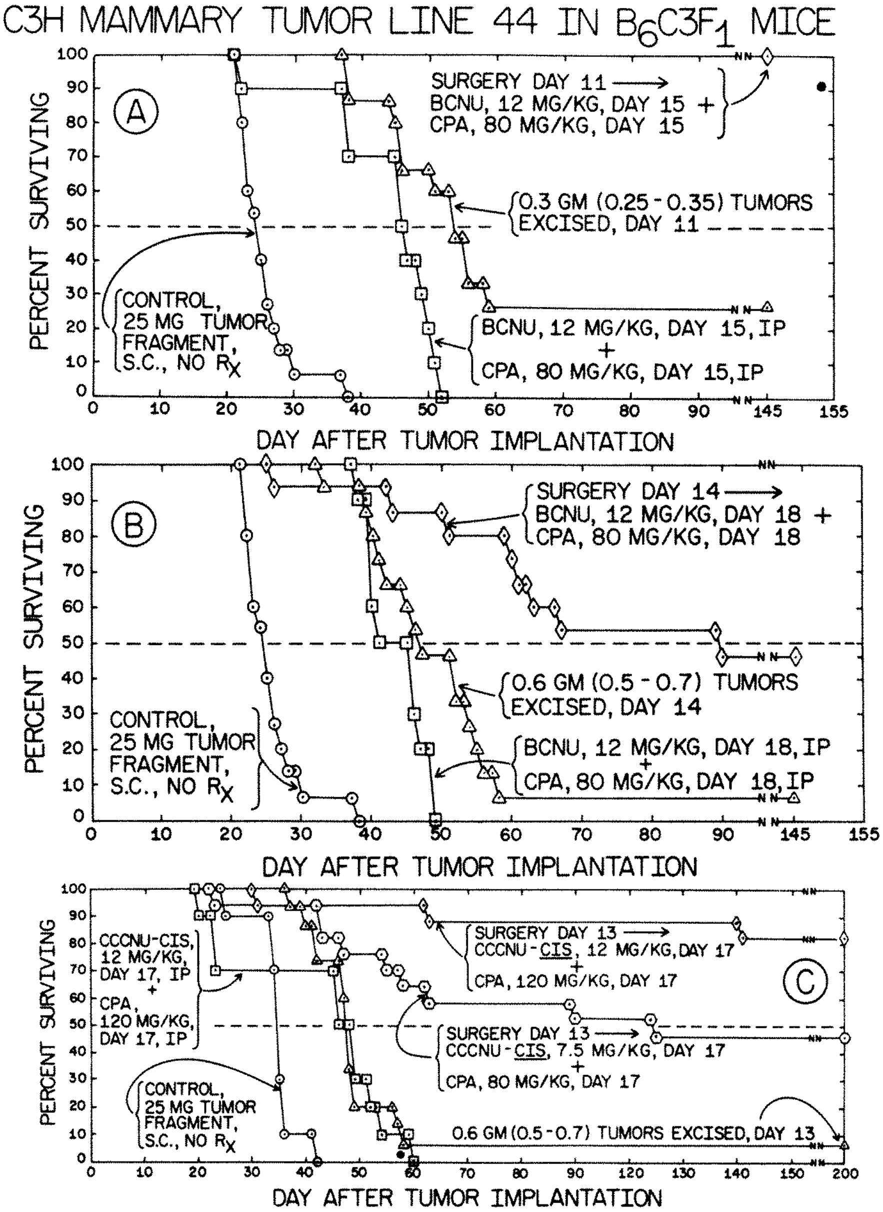

Fig. 5. Curative surgical adjuvant chemotherapy of C3H mammary adenocarcinoma. Influence of tumor staging and drug dosage on cure rates. (*A*) Surgery on day eleven (about 30 percent cured) or BCNU+CPA on day 15 (no cures); surgery followed by adjuvant drug treatment (100 percent cured). (*B*) Surgery delayed to day 15 (less than ten percent cured) or BCNU+CPA on day 18 (no cures); surgery followed by adjuvant drug treatment (about 50 percent cured). (*C*) Surgery on day 13 (less than ten percent cures) or drug treatment (CCCNU-*cis*+CPA) on day 17 (no cures); surgery on day 13 followed by drug treatment on day 17 (about 80 percent cured with high drug doses and 50 percent cured with low drug doses).

percent with surgical adjuvant chemotherapy (Fig. 5*A*) and from less than ten percent to about 50 percent with surgery on day 14 and chemotherapy on day 18 (Fig. 5*B*). Dose response of curative surgical adjuvant chemotherapy with CCCNU-*cis* plus CPA is illustrated in Figure 5*C*.

Colon Tumor, Line 26 (Fig. 6, *A* and *B*).[10] This is a metastasizing, uniformly fatal, if untreated, *N*-nitroso-*N*-methylurethane-in-

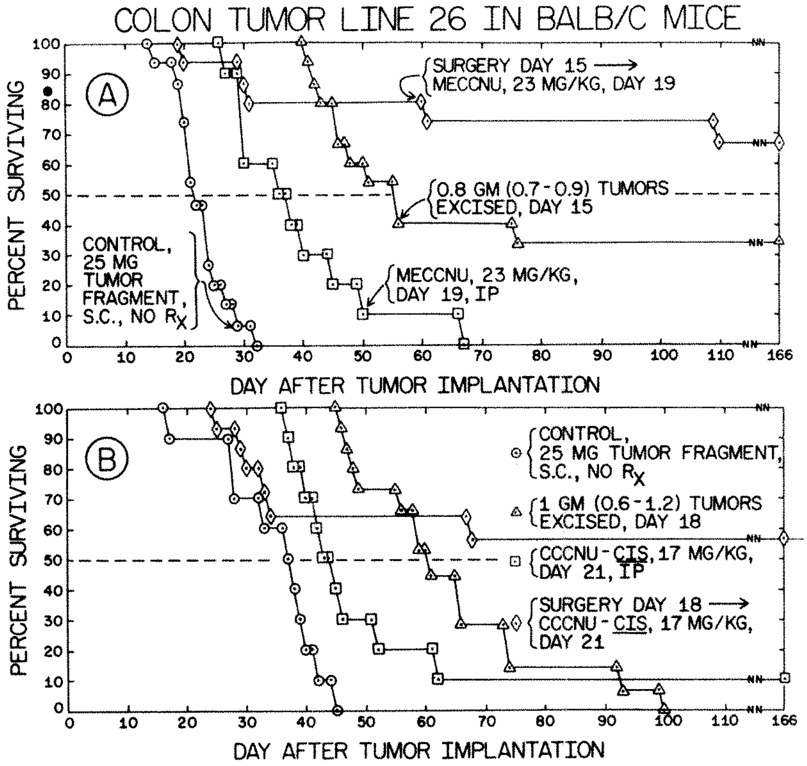

Fig. 6. Curative surgical adjuvant chemotherapy of colon tumor Line 26. Influence of tumor staging on cure rates. (*A*) Surgery on day 15 (35 percent cured) or MeCCNU on day 19 (no cures); surgery on day 15 followed by MeCCNU on day 19 (65 percent cured). (*B*) Surgery on day 18 (no cures) or CCCNU-*cis* on day 21 (ten percent cured); surgery followed by CCCNU-*cis* (more than 50 percent cured).

duced, transplantable, colon tumor of mice.[9]

Surgical removal of the primary tumor on days 15 to 18 postimplant resulted in 35 to 100 percent failure to cure. Treatment with MeCCNU (Fig. 6*A*) or CCCNU-*cis* (Fig. 6*B*) four days after surgery significantly increased long-term cure rates (55 to 65 percent cures).

The above data illustrate some basic principles of effective surgical adjuvant chemotherapy:

1. Effective therapeutic response to drug treatment is directly related to total body burden of tumor cells. Drugs marginally effective or ineffective in treating advanced primary tumors and their resultant metastases may be curative for the lower body burden of only the metastatic foci (Fig. 3; 4, *A* and *B*; 5, *A–C*; and 6*A*).

2. Maximal (high dose) drug treatment, consistent with acceptable toxicity to vital normal cells, is indicated because metastatic tumor cell burdens show dose responsiveness to effective drugs (Fig. 5*C*).

In addition to the improved cure rates using surgical adjuvant chemotherapy in treating the four transplantable murine tumors discussed above, Fugmann *et al.*[7] have reported the cure of a metastasizing spontaneous mammary carcinoma in mice with multidrug surgical adjuvant chemotherapy. Some cures were obtained with surgery alone, but these cure rates were significantly increased with adjuvant chemotherapy.

C. *Radiation Adjuvant Chemotherapy.*

Very little work has been done up to this time, either by laboratory investigators or clinicians, with radiation adjuvant chemotherapy to control likely metastases asso-

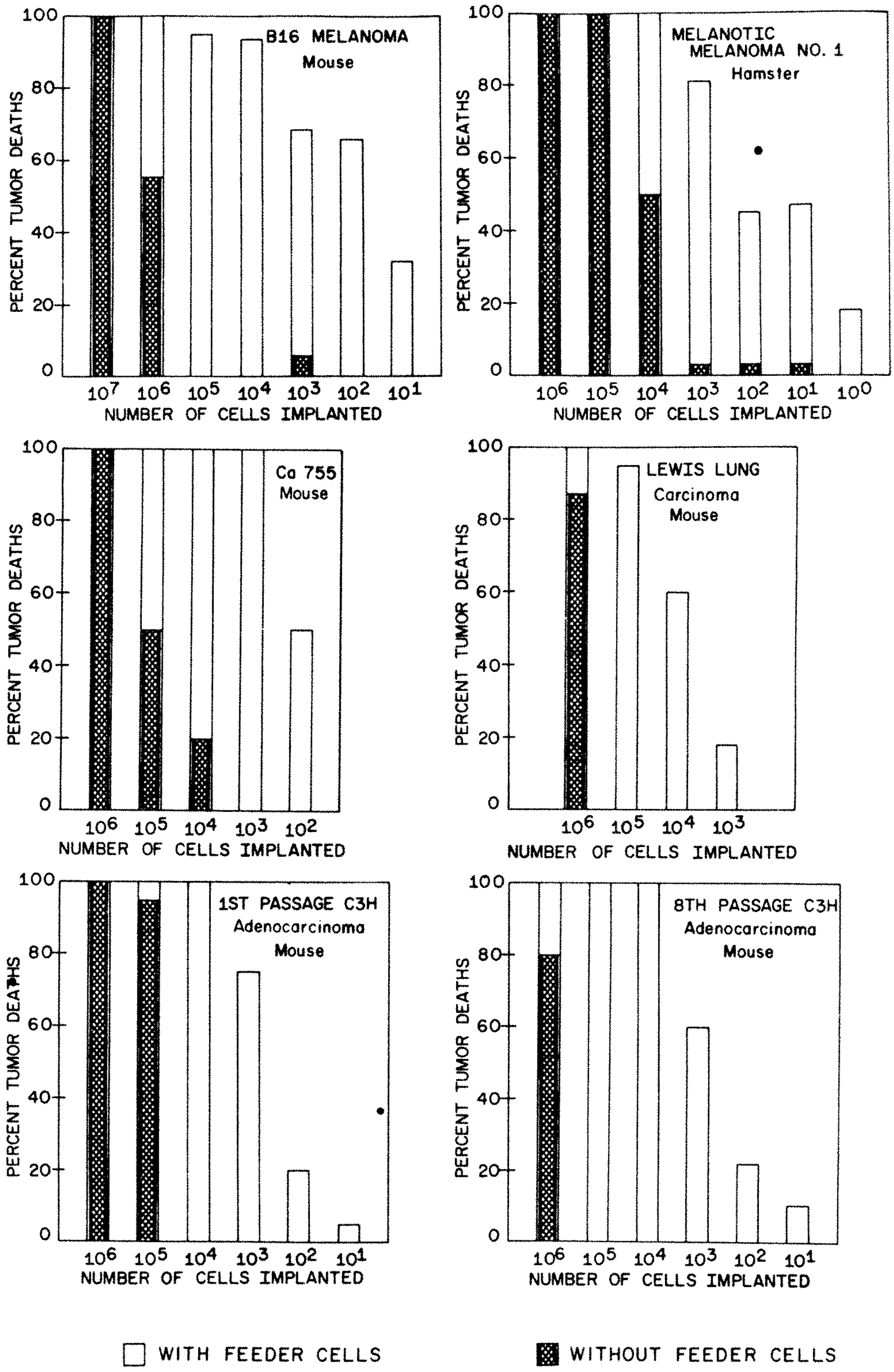

Fig. 7. Growth of rodent tumors following subcutaneous implant of counted numbers of tumor cells, with and without feeder cells. Hemocytometer-counted freshly prepared tumor cells were suspended in 0.5 ml of Locke's solution plus five percentglucose (without feeder cells) or in 0.5 ml of a 20 percent w/v brei of radiation-inactivated (10,000 r from Co^{60}) homologous tumor cells (with feeder cells). There were about 10^8 feeder cells weighing about 100 mg in each implant (assuming 10^9 tumor cells/gram).
(Reproduced with permission of *Cancer*)[30].

ciated with advanced primary tumors which may be effectively but not curatively treated with radiation.[5]

It seems logical to assume, however, that the basic principles outlined above for curative surgical adjuvant chemotherapy should obtain in a similar manner for radiation adjuvant chemotherapy.

EFFECT OF INACTIVATED TUMOR ON REMAINING CELLS

The presence of radiation-inactivated tumor cells has been reported to markedly increase the cloning efficiency of human cervical carcinoma (HeLa) cells *in vitro*.[23] Radiation-inactivated Ehrlich ascites tumor cells[24] and radiation-inactivated tumor cells from a number of spontaneous murine mammary tumors, methylcholanthrene-induced murine sarcomas, and a murine ascites lymphoma have been reported to stimulate growth of small viable homologous tumor cell populations.[25,26] Experimental studies at Southern Research Institute have quantitated the support of radiation-inactivated homologous tumor cells for viable tumor cell populations *in vivo* with B16 melanoma,[11] adenocarcinoma 755,[11] Lewis lung carcinoma,[21] and C3H adenocarcinoma[11] in mice and with a melantoic melanoma of hamsters.[11] Dilutions of these tumor cells were suspended in radiation-inactivated homologous tumor cell brei (with feeder cells) or noncellular diluent (without feeder cells), and these preparations were implanted subcutaneously into susceptible mice or hamsters. Results of these experiments are shown in Figure 7. The presence of radiation-inactivated tumor cells resulted in growth of lethal tumors with fewer viable tumor cells by 3–5 powers of ten than without feeder cells.[30] These data suggest that curative radiation therapy in individual tumor foci may be more difficult than curative surgical removal when small numbers of viable tumor cells are left *in situ*. They further suggest that regrowth may occur in irradiated tumor masses containing very small numbers of residual viable tumor cells. Surgeons may encounter a similar problem, however, since it has been reported that transplanted syngeneic normal cells (lung, liver, kidney) which do not grow on transplant, similarly increase tumor growth rates with small numbers of implanted Lewis lung carcinoma cells.[4] It is possible that traumatized normal cells resulting from surgical manipulation could serve as feeder cells supporting the growth of small numbers of viable tumor cells left *in situ* at time of surgery.

The problem of radiation-inactivated tumor cell support of growth of very small numbers of residual viable tumor cells may also carry a therapeutic asset, since significant cytotoxic immunity has been demonstrated following injection of radiation-inactivated homologous tumor cells with several animal tumors. The relative importance of feeder cell stimulation and acquired immunologic suppression of residual viable tumor cells in tumor cell populations incompletely inactivated by radiation has not been clearly shown, but it is a subject worthy of investigation.

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OPTIMAL VISUALIZATION OF ESOPHAGEAL VARICES*

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ABSTRACT:

Twelve patients with known esophageal varices and willingness to cooperate were included in the study. Medications administered were placebo, 2 mg of glucagon, and 30 mg of propantheline bromide. All medications were given double-blind and crossover.

On the basis of this study the authors believe that for optimal visualization of esophageal varices the following is the procedure of choice: (1) the patient should remain horizontal (this is best done in the left lateral position for comfort and ease of expectoration) for ten minutes after swallowing high density barium; (2) the patient should "clear his throat" frequently and expectorate all saliva (barium sticks to the pharynx and makes the patient want to swallow and "clearing his throat" by forced expiration helps the patient to expectorate this coating and prevents swallowing); (3) filming should be done in expiration in the supine (left posterior oblique to table top) position; and (4) in equivocal cases the examination can be repeated with an anticholinergic drug if the patient has no contraindications to its use. The patient should empty his bladder just before administration of the drug. The intelligent use of these factors should result in a saving of both fluoroscopic time and film, and give the radiologist a safe optimal diagnostic yield.

VARICES of the esophagus were first demonstrated roentgenologically by Wolf[26] in 1928. Schatzki[23,24] in 1931 and 1933, and Bediczka and Taschakert[4] in 1932 described the classical roentgenographic findings. The roentgen diagnosis of varices still depends on the demonstration of: (1) nodular filling defects in the distal third of the esophagus, which may or may not be persistent; (2) widened tortuous or worm-like mucosal folds with a scalloped contour; or (3) Bediczka and Taschakerts'[4] classic "string of pearls" defect. Despite these well known and widely accepted roentgenogrghic criteria, esophageal varices continue to escape diagnosis in standard barium studies. Roentgenographic accuracy of diagnosis ranges from 15 percent to 63 percent of varices seen endoscopically.[3,22]

The disparity between the varices seen endoscopically and those identified roentgenographically has prompted the radiologist to develop numerous techniques and maneuvers to increase the diagnostic yield. Nathan[18] advocated the engorgement of varices by occlusion of the venous outflow with an inflated balloon placed in the midesophagus. The technical difficulties and dangers inherent in the use of the Sengstaken tube also apply to this method. Fluoroscopic examinations with the patient in the horizontal oblique position with "blocked" deep inspiratory views (Valsalva) and Müller maneuvers, even following intravenous intravascular volume expansion, have all been attempted without consistent success.[5] This lack of consistent success may reflect dissatisfaction with examination time, effort, and patient discomfort. More recently the enlargement of varices under endoscopic visualization has been reported following the injection of propantheline bromide.[9] Pruszynski[22] and Dalinka *et al.*[9] have shown enhanced roentgenographic visualization of esophageal varices using Buscopan and propantheline bromide in patients with liver disease or equivocal varices.

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When esophageal varices are present, it is most important that the radiologist be able to make the diagnosis. The roentgenographic procedure is simple, is safe, has excellent patient acceptance, and is relatively easy to do. Because of this and the varying comments in the literature, it was decided to study various roentgen methods to determine: (1) whether keeping the patient recumbent for a period of time was of value; (2) the position in which the most diagnostic roentgenogram is obtained; (3) the optimal phase of respiration; and (4) whether drugs aided in the demonstration of esophageal varices.

MATERIAL

Twelve adult men with known varices, 42 to 61 years of age, averaging 52.5 years, and willing to cooperate and give informed consent were included in the study. All subjects were fully informed according to the spirit and to the letter of the Declaration of Helsinki. Patients on anticoagulant therapy or those who had a history of possible pheochromocytoma, insulinoma, previous myocardial infarction and sensitivity or reactions to glucagon or propantheline bromide were excluded. No medication nor antacid had been given during the previous twelve hours and none of the patients was receiving anticholinergic drugs. Patients with partial urinary bladder-neck obstruction, ileus, and glaucoma were also excluded from the study. Eleven of the patients were known alcoholics with Laennec's cirrhosis and one patient probably had postnecrotic cirrhosis. The cases presenting with a history and physical findings typical of cirrhosis are summarized in Table I. In the final analysis there were two patients with enormous, six with very large, three moderately large, and one with small esophageal varices.

Table I

NUMBER OF PATIENTS PRESENTING WITH THE FOLLOWING HISTORY AND PHYSICAL FINDINGS

History and Physical Findings	Present	
	Yes	No
History:		
Previous bleeding (varices)	2	10
Bleeding on admission (varices)	3	9
Delirium tremens	3	9
Seizures	2	10
Physical Findings:		
Spider angiomata	8	4
Umbilical hernia	3	9
Ascites	5	7
Abdominal veins visible	5	7
Palpable liver	8	4
Palpable spleen	3	9
Palmar erythema	8	4
Dupuytren's contracture present	2	10
Shoulder atrophy	6	6

METHOD

Medications included placebo (2 ml of diluting solution for glucagon), 2 mg of glucagon, and 30 mg of propantheline bromide in 2 ml of sterile water. Medication was given intramuscularly as one dose, double blind, and crossover. Drugs were given at intervals of at least three days. Patients were assigned the next medication sequence, without constraints, as they were entered into the study.

On the morning of the test the patients fasted; unless the study was done in the afternoon, in which case they were allowed a light breakfast that morning and no lunch. Each patient was instructed to empty the bladder prior to starting the study. The pulse rate per minute, blood pressure, and pupil size in millimeters were measured.

Prior to medication the patient was given two good swallows, approximately 60 ml of 200 percent weight/volume barium sulfate,* and the following roentgenograms of the esophagus were obtained: supine (right anterior oblique to screen), one spot film at inspiration, and one spot film at expiration; prone (left posterior oblique to screen), one spot film at inspiration and one at expiration. All films were appropriately marked after each filming. Throughout the entire examination the patient remained horizontal on the x-ray table in quiet respiration. This was done since all patients can be examined in the horizontal position, but many cannot stand because of recent hemorrhage. The patient was instructed to expectorate all saliva into a cup or kidney basin that was provided. Occasionally a patient accidentally swallowed some saliva, and an additional swallow of barium was given when needed for visualization. Swallowing with its attendant peristalsis tends to strip the blood from the varices. Immediately after the initial roentgenograms were obtained, the patient was given one of the medications intramuscularly. Five minutes after injection, supine films were obtained at inspiration and expiration. Ten and 20 minutes after injection, supine and prone films were obtained at inspiration and expiration as obtained initially. All roentgenograms were reviewed immediately on completion of a study on any one day to ascertain that the required study had been obtained.

When the final roentgenograms were obtained, the pulse rate per minute, blood pressure sitting, and pupil size in millimeters were again measured. At this time the patient was told that he would be questioned the following day concerning the presence of symptoms of nausea, vomiting, abdominal distress, headache, dizziness, flushing, slowed urinary stream, dysuria, urinary retention, and dryness of the mouth. If a symptom occurred within six hours after the injection of the drug, he was asked to quantitate the intensity of the symptoms according to a score of one to four (0—none, one—mild, two—moderate, three—moderately severe, and four—severe). At the completion of the study, all 504 roentgenograms were read by the radiologist at one sitting. The films were arranged for each patient in the order taken. At this time the radiologist: (1) estimated the visualization of the esophageal varices according to a score of one to five (one—not seen, two—equivocal, three—present but poorly seen, four—well visualized, and five—excellent visualization); (2) estimated the size of the largest varices seen on a score of one to five (one—not seen, two—small, three—moderately enlarged, four—very large, and five—enormous); (3) estimated the barium coating of the esophagus as one to five (one—none, two—poor, three—fair, four—good, and five—excellent); and (4) determined whether he thought the medication affected the study of the esophagus, with a score of one to five (one—made worse, two—no change, or improvement, three—fair, four—good, and five—excellent).

For each subject every film was evaluated for: (1) visualization of the varices and barium coating and scored 0 to four (0—none, one—poor, two—fair, three—good, and four—excellent); (2) whether the medication helped in the study was scored as 0 to four (0—none, one—a little, two—some, three—a lot, and four—excellent); (3) the width of the esophagus measured in centimeters; and (4) the width of the varices measured in millimeters.

The roentgenograms were read by two radiologists without knowledge of the drugs given. Each radiologist read the roentgenograms at a time separate from the other so that each "reading" was distinct and separate without consultation. Each set of treatment films was compared and recorded from one (best) to three (poorest). The responses of each radiologist were analyzed

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Table II*

Visual Estimates	Medications		
	Placebo	Glucagon	Propantheline Bromide
Read by Dr. Roscoe E. Miller			
1. Visualization of varices			
Before treatment	3.17	3.33	3.00
After treatment	4.00	3.75	4.50‡
2. Size of varices	3.50	3.42	3.67
3. Barium coating	4.00	4.25	4.25
4. Medication was of value	3.17	2.92	4.42†‡
Read by Dr. Edward Cockerill			
1. Visualization of varices			
Before treatment	3.00	3.17	2.83
After treatment	4.08	3.67	4.42‡
2. Size of varices	3.08	3.08	3.08
3. Barium coating	3.50	3.83	3.58
4. Medication was of value	3.08	2.67	3.83‡

Scores

(1) 1—not seen, 2—equivocal, 3—present but poorly seen, 4—well visualized, and 5—excellent visualization

(2) (largest seen) 1—not seen, 2—small, 3—moderately enlarged, 4—very large, and 5—enormous

(3) 1—none, 2—poor, 3—fair, 4—good, and 5—excellent

(4) 1—made worse, 2—no change or improvement was, 3—fair, 4—good, and 5—excellent

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* Average scores for over-all estimates of visualization and size of varices, adequacy of the barium coating and whether medication helped in the visualization of the varices as read by two independent radiologists.

† Placebo *vs.* propantheline bromide $p < 0.05$.

‡ Glucagon *vs.* propantheline bromide $p < 0.05$.

separately. However, since the results were similar, the reading by R.E.M. will be discussed (Table II).

RESULTS

An analysis of variance was used to evaluate the response to the three treatments. The residual variability was used to compare the three treatments on a pair-wise basis for each investigator using Tukey's multiple range test at the 0.05 level. In the over-all estimate of response, when propantheline bromide was given as compared to placebo administration, the radiologist reported that the medication definitely ($p<0.05$) helped him to visualize the esophageal varices.

Following the administration of propantheline bromide as compared to placebo or glucagon, visualization of the varices was improved ($p<0.05$) in the supine expiration, prone inspiration and expiration views; width of the varices was increased ($p<0.05$) in the prone inspiration and expiration views; width of the esophagus was increased ($p<0.05$) in the supine and prone inspiration and expiration views; and the medication was considered to have helped ($p<0.05$) the radiologist to see the varices better in the supine and prone inspiration and expiration views of the esophagus. The average width of the varices in millimeters and the radiologist's estimate of whether the medication helped, for all medications, are presented graphically in Figures 1, *A–C*; and 2, *A–C*. There was no change in the barium coating that could be attributed to the drugs.

Roentgenograms of patient W. L. taken during the supine expiration when on

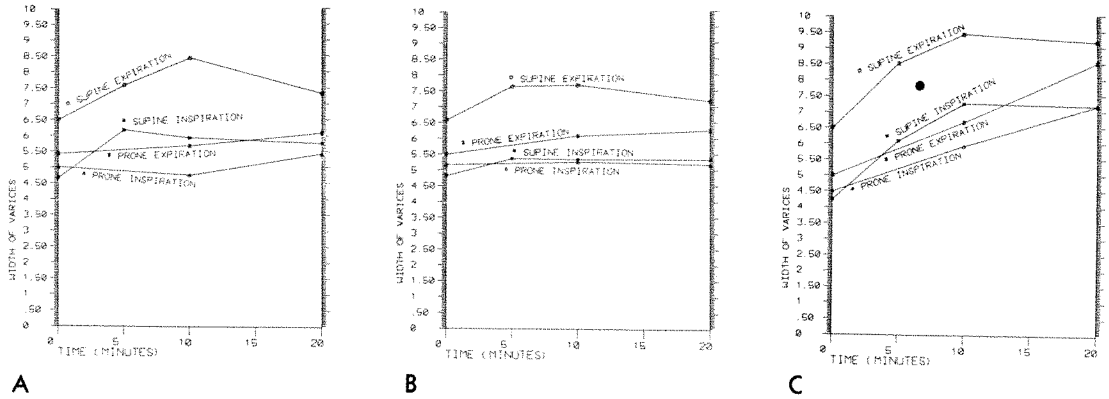

FIG. 1. Computer read-outs of the width of varices in millimeters. (*A*) Placebo. (*B*) Glucagon. (*C*) Propantheline bromide. Measurements were taken at 0, 5, 10, and 20 minutes.

placebo and propantheline bromide show the effect of time (Fig. 3, *A* and *B*). The prone (left posterior oblique) and supine (right anterior oblique) roentgenograms of patient C.H., when on placebo and propantheline bromide, demonstrate the effect of respiration and position (Fig. 4, *A* and *B*). The supine (right anterior oblique) roentgenograms of W.L. after placebo and after propantheline bromide in inspiration demonstrate the effect of the phase of respiration (Fig. 5, *A* and *B*). The supine ten minute roentgenograms of C.B. and W.L. after each medication show the effect of drugs (Fig. 6, *A* and *B*). The initial roentgenograms taken of R.M. in prone and supine inspiration show that varices can be easily missed (Fig. 7*A*). Commonly, many patients are only observed and filmed in inspiration. Roentgenograms taken at ten minutes of patient R.M. in supine expiration after placebo, glucagon, and propantheline bromide are presented in Figure 7*B*. These roentgenograms demonstrate the effectiveness of time, position, respiration, and drug to enhance visualization of esophageal varices.

In answer to the initial questions asked of the study, the data indicate that: (1) in the horizontal position maximum engorgement of esophageal varices occurred in approximately ten minutes; (2) that all

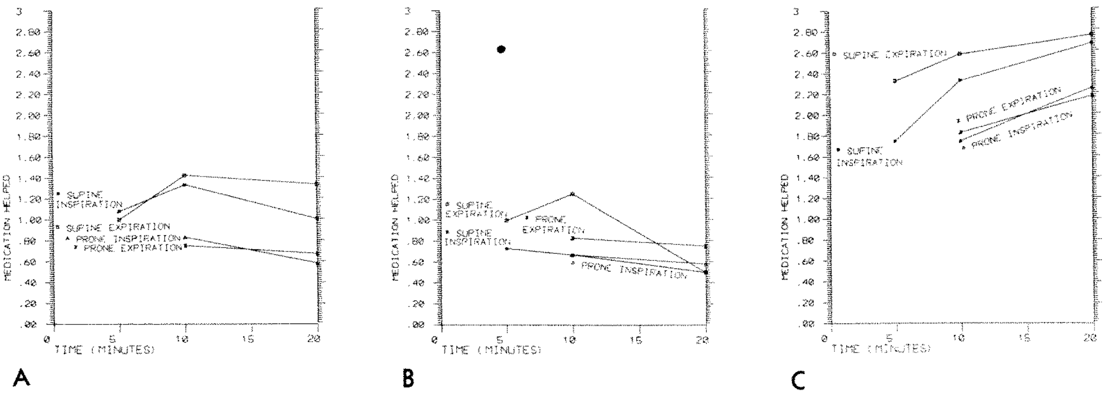

FIG. 2. Computer display of whether the medication aided the radiologist in the demonstration of varices. The graphs compare preliminary (0 time) films with films at 5, 10, and 20 minutes. (*A*) Placebo. (*B*) Glucagon. (*C*) Propantheline bromide. In (*C*) propantheline bromide optimizes the identification of varices in all parameters of the study.

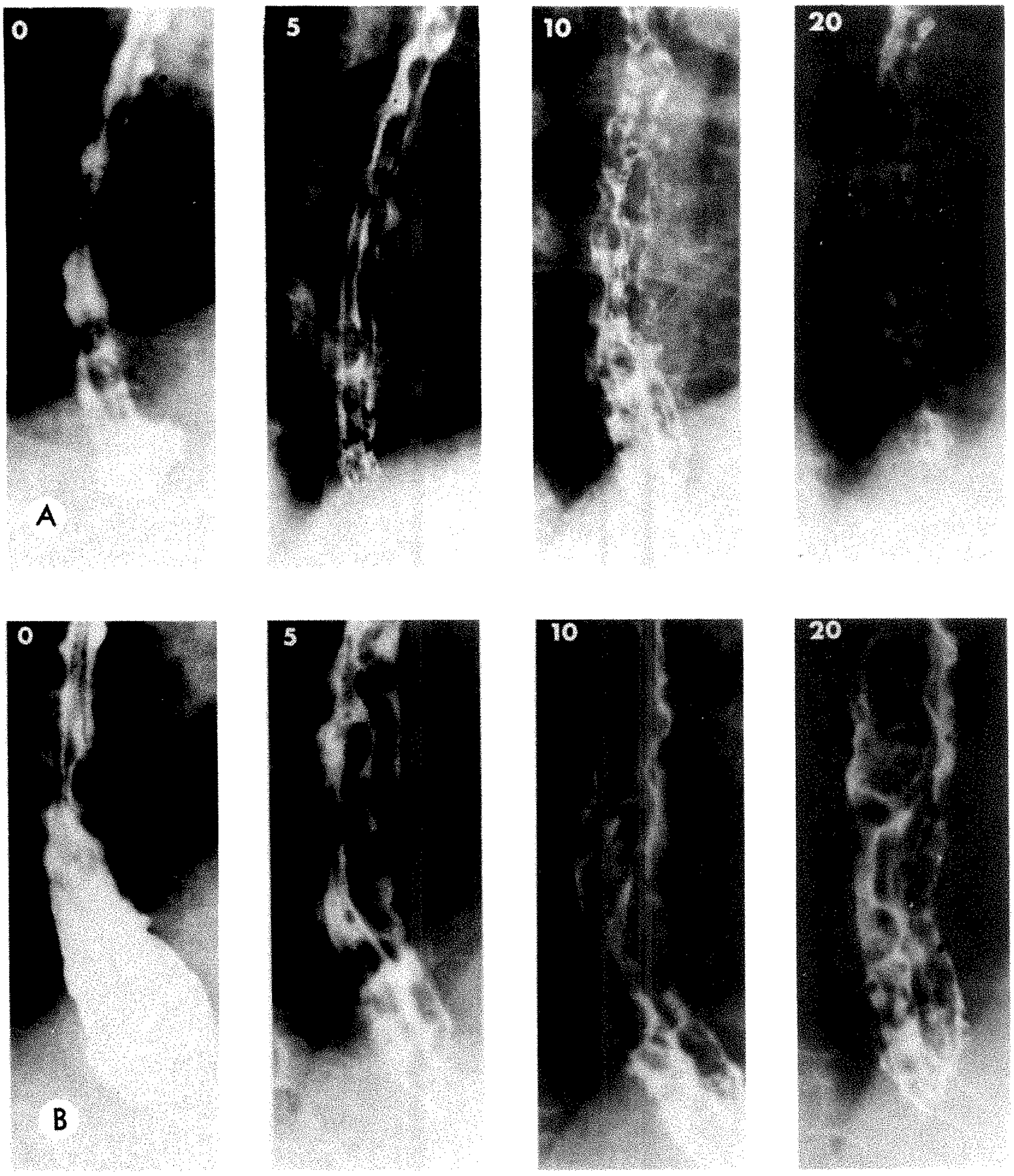

Fig. 3. The effect of time. Roentgenograms of patient W.L. taken during supine expiration at 0, 5, 10, and 20 minutes. (*A*) Placebo. (*B*) Propantheline bromide.

the roentgenograms of the esophagus taken with the patient in deep expiration were superior to the inspiratory views, and that the most diagnostic view was the supine (right anterior oblique) expiration ten minute film; and (4) the esophageal varices were more easily visualized, and the esophagus was wider after propantheline bromide than after either of the other two drugs.

The pulse and blood pressure were obtained initially and on completion of the study. When propantheline bromide was given, as compared to placebo or glucagon, there was an average increase ($p < 0.05$) of 22 beats per minute in the pulse rate. There were no changes in the blood pressure or

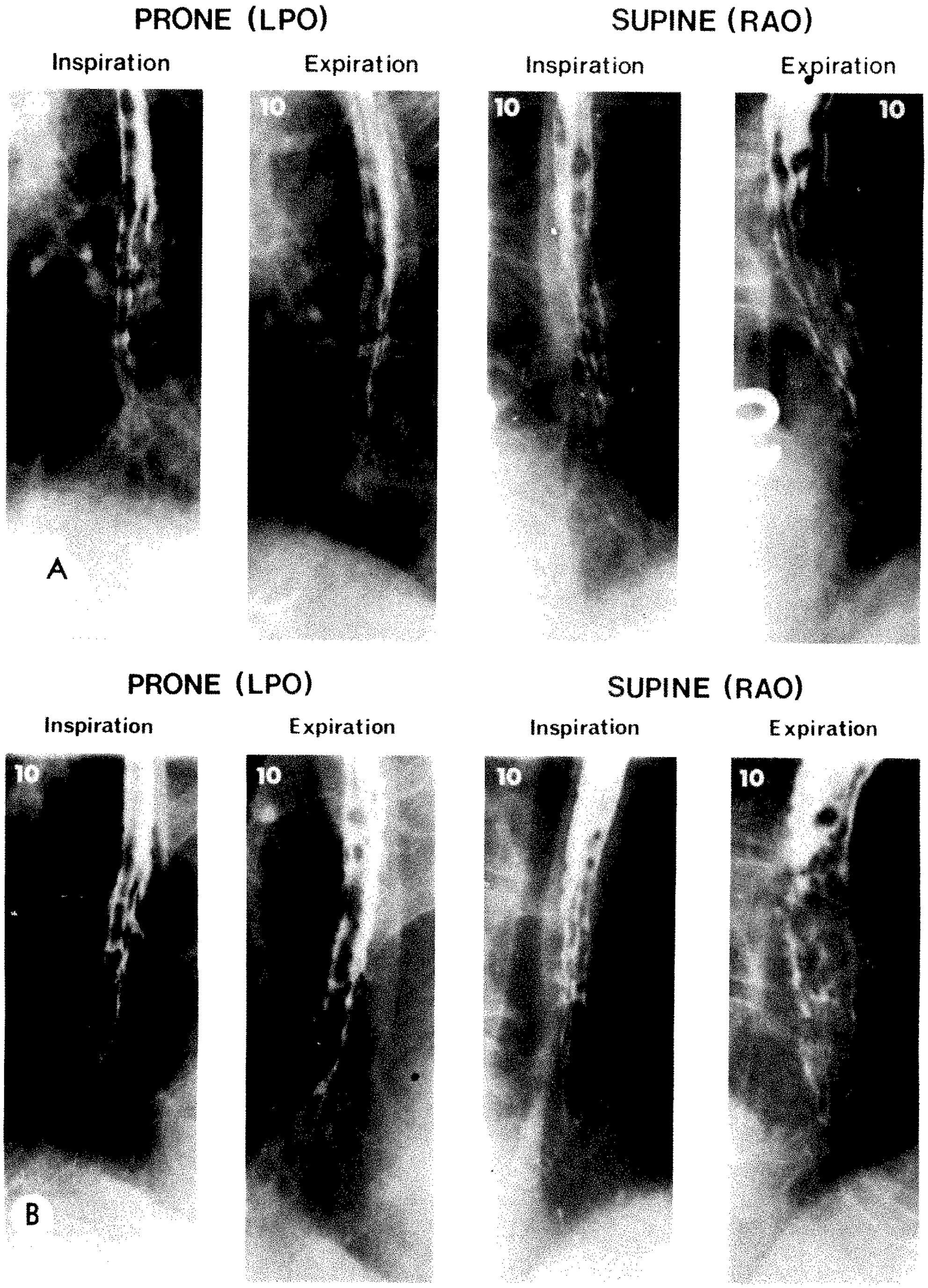

Fig. 4. The effects of position. Roentgenograms of patient C.H. with placebo (*A*), and propantheline bromide (*B*), in prone and supine positions. Note that the supine expiration roentgenogram shows the varices to the best advantage.

pupillary size that could be attributed to any of the drugs given. The patients were also questioned concerning certain side effects. When placebo was given there were three reports each of dryness of the mouth and dizziness, and one of dysuria with a total score of ten; after glucagon there were two reports of dryness of the mouth and one of dizziness with a total score of six; and after propantheline bromide there were six reports of dryness of the mouth and one each of nausea, vomiting, headache, dizziness, flushing, slowed urinary stream, and blurring of vision with a total score of 26.

DISCUSSION

Using standard roentgenographic techniques esophageal varices are diagnosed in 63 percent of the cases shown by endoscopy. Roentgenologic identification of varices in only 55 percent of 164 individuals with endoscopically proved varices with failure to identify 25 percent of those cases with endoscopically large and 75 percent of cases with endoscopically small varices was reported by Dagradi *et al.*[8] Recently, Pruszynski[22] reported a diagnostic accuracy of 63 percent in 55 patients with portal hypertension which increased to 98 percent (54/55) when spasmolytic agents were administered. Several investigators have since reported that anticholinergic drugs appear to enhance the identification of esophageal varices. Dalinka and associates[9] reported enhanced variceal visualization using propantheline bromide in patients with previously equivocal esophagograms. Ghahremani *et al.*[11] reported that the results of their use of atropine sulfate and propantheline bromide were excellent. They state that they were able to identify 100 percent of patients with subsequently proved varices. More recently Uthgenannt and associates[25] indicated that when using Buscopan there was increased roentgenologic visualization of varices in patients with cirrhosis. We agree with Dalinka and associates[9] that the frequent use of anticholinergic premedication for patients undergoing endoscopy is one of the reasons for the increased diagnostic yield of endoscopic studies.

In 1957 Nelson[19] reported that muscle contraction and peristalsis can force blood from varicosities and render them roentgenographically invisible. He recommended the use of atropine sulfate primarily to dry up secretions which ordinarily would be swallowed and to improve distal esophageal coating. The decrease in swallowing by reducing the production of saliva not only diminished the washing away of the barium with the saliva but also decreased the

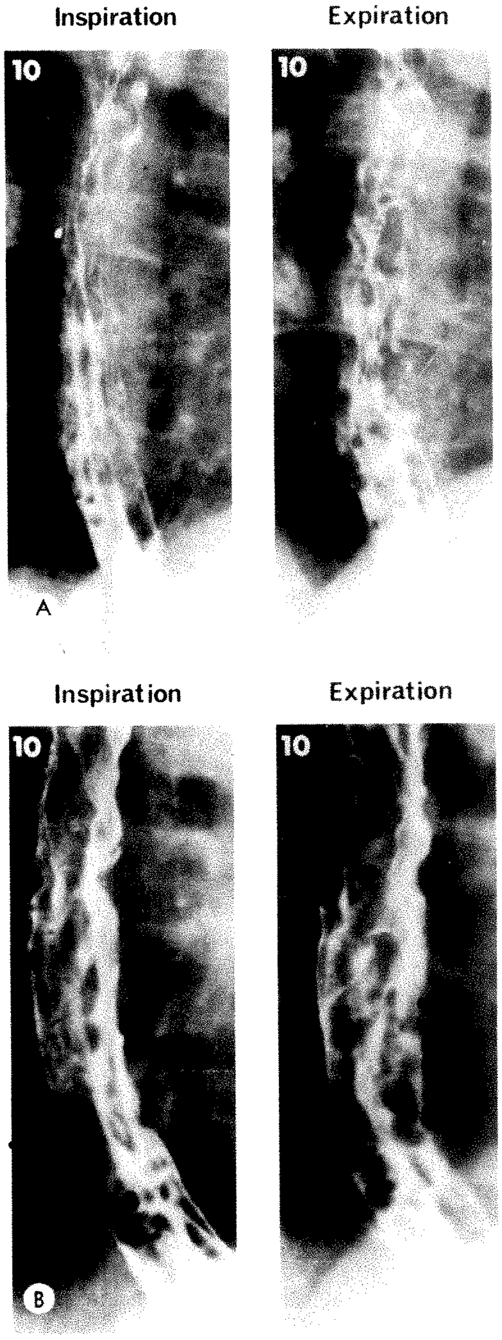

Fig. 5. The effects of respiration. (*A*) Placebo. (*B*) Propantheline bromide. Both demonstrate that varices show best in expiration.

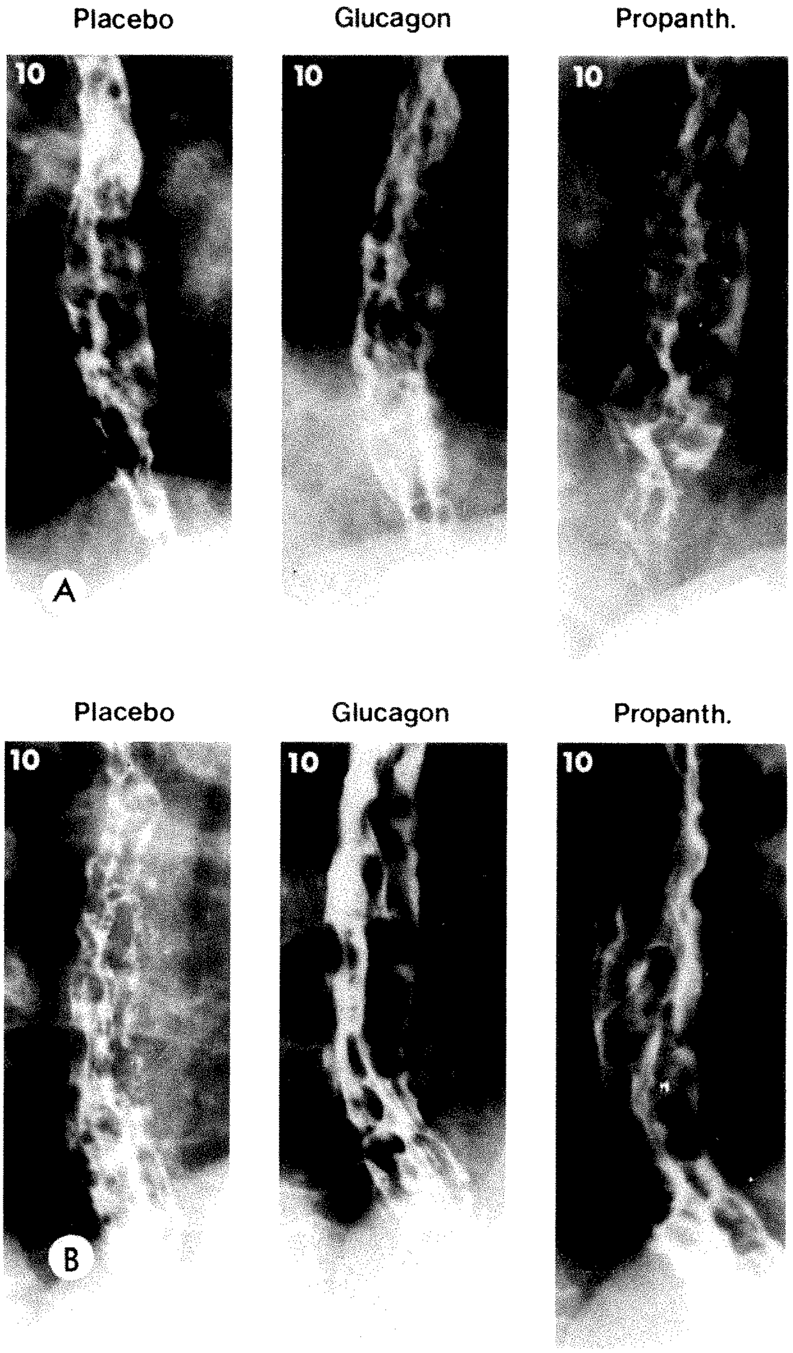

FIG. 6. (*A* and *B*) The effects of drugs. Patients W.L. and C.H. are shown with placebo, glucagon, and propantheline bromide.

stripping of the blood from the varices by peristalsis. The peristaltic contractions of the body of the esophagus are probably controlled by cholinergic nerves. The intrinsic innervation of the esophagus is mainly cholinergic[1] and contractions are inhibited by atropine.[14] Interestingly, the amplitude of the esophageal peristaltic waves is unaffected by penta-gastrin,[13] suggesting that the esophageal body muscle, in

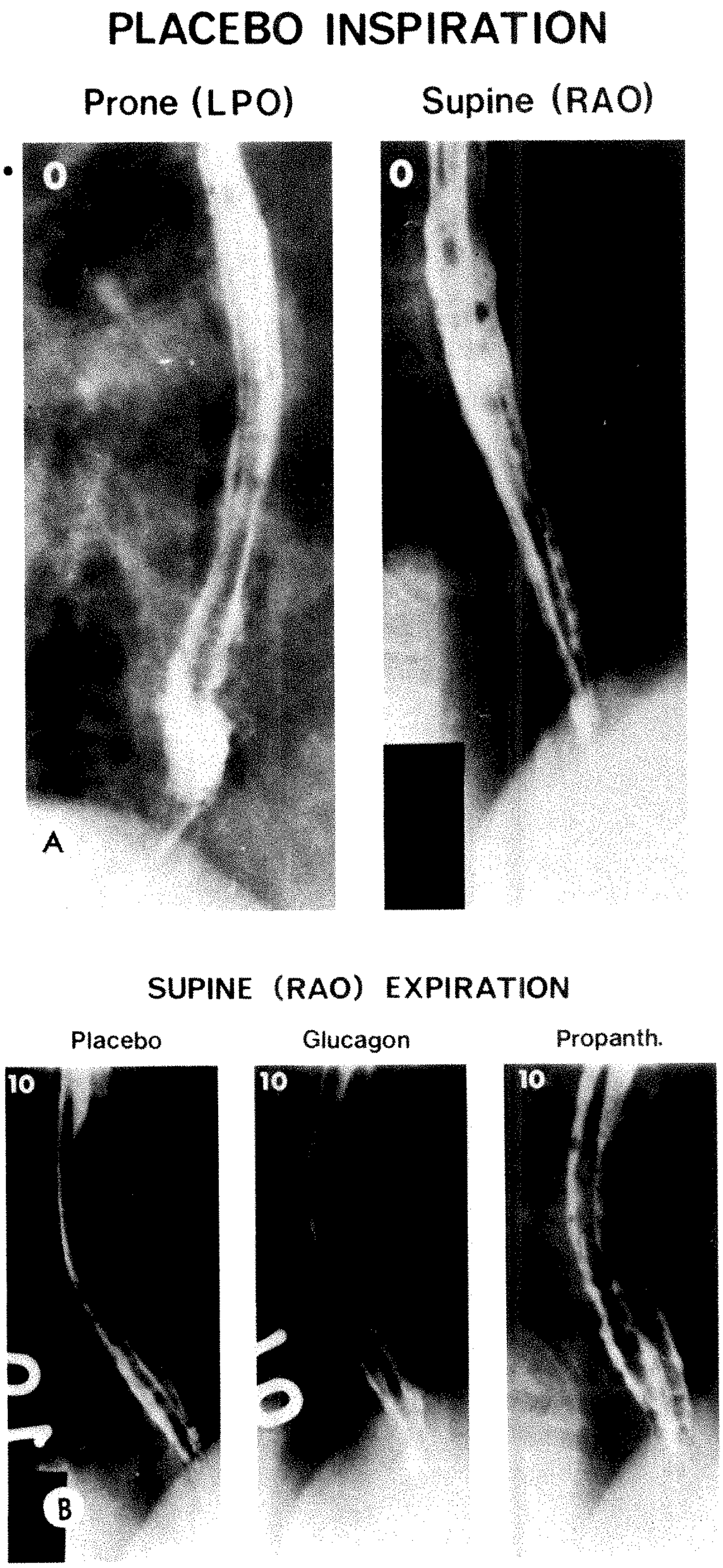

FIG. 7. Patient R.M. (*A*) The initial roentgenograms in prone and supine inspiration demonstrate that the varices can easily be missed. (*B*) The effects of placebo, glucagon, and propantheline bromide at ten minutes in supine expiration all demonstrate varices. The effects of the drugs are easily seen and should be compared with (*A*).

contradistinction to the lower esophageal sphincter muscle, is quite insensitive to this hormone.[7] This implies that the esophageal body muscle is relatively incapable of responding to polypeptide hormones such as glucagon. In a recent study Hogan *et al.*[12] reported that although glucagon relaxed the lower esophageal sphincter it had no effect on esophageal peristalsis. Thus, although glucagon has been reported to increase mesenteric and portal blood flow significantly, there was no evidence that this was of help in the demonstration of varices roentgenographically. The enhanced visualization by propantheline bromide may therefore be entirely secondary to muscular relaxation of the esophageal body.

Glucagon has been proved to be effective and safer than anticholinergic drugs for the pharmacoradiology of the stomach, small bowel, and colon.[16,17] However, in this and other studies the esophagus, unlike the rest of the gut, has been proved to be quite insensitive to gastrointestinal hormones.[7,127,13] On the other hand, the esophagus is innervated by cholinergic nerves, and contractions can be inhibited by anticholinergic drugs. Therefore, if a drug is needed, an anticholinergic agent such as used in this study seems preferable for the demonstration of esophageal varices. However, the use of anticholinergic drugs is not recommended in patients with a history of glaucoma, previous myocardial infarction, partial urinary bladder-neck obstruction, ileus, and sensitivity to the drug.

We have shown that time, position, the phase of respiration, and medication are all additive factors in the demonstration of esophageal varices. On the basis of this study we believe that in most cases the optimal use of the factors of time, position and the phase of respiration will demonstrate esophageal varices without the use of drugs. The proper use of these factors by the radiologist will result in a saving of both fluoroscopic time and film and assure him an optimal diagnostic yield.

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INVOLVEMENT OF THE GASTRIC ANTRUM IN MÉNÉTRIER'S DISEASE*

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ABSTRACT:

Thirteen cases of Ménétrier's disease from the files of the Armed Forces Institute of Pathology that could be documented pathologically and correlated with appropriate roentgenograms were analyzed for the distribution of folds. Enlarged folds occurred in a localized area or in several areas simultaneously. The greater curvature of the body was most often involved (77 percent), but the antrum was affected in almost one-half (46 percent) of the cases; thus, the concept of relative antral sparing is not valid, and the diagnosis should be considered when there is gastric rugal enlargement in any distribution. The condition seems to be classified best as a hyperplastic gastropathy rather than a hypertrophic gastritis.

MÉNÉTRIER described the condition that bears his name in 1888.[4] It is a disease of middle-aged men. Complaints are pain, vomiting, and weight loss. Hypoproteinemia, multiple endocrine tumors, and the Zollinger-Ellison syndrome have been associated with it. Other names given to this disease include hypertrophic gastritis, giant mucosal hypertrophy, cystic gastritis, and hyperplastic gastropathy. All these terms, which probably describe the same roentgenologic, gross, and histologic appearance, have resulted in a certain degree of confusion in the literature. Is this process a gastritis or a gastropathy; a hypertrophy or a hyperplasia?

There has been little written recently about the roentgenologic features of Ménétrier's disease. Reese *et al.*[5] reported a series of 18 cases, including gross, microscopic, and roentgenographic descriptions. They suggested four criteria (size of folds, configuration of greater curvature, thickness of the gastric wall, and mucus mixing) for making the roentgenologic diagnosis of Ménétrier's disease. Fieber[2] relied more on disordered motility causing a delay in emptying time to suggest the diagnosis. There has been no adequate roentgenologic study of the distribution of the enlarged folds, but it is generally felt that the greater curvature of the body is most often involved and that there is relative sparing of the gastric antrum.

It is the purpose of this paper to describe the roentgenologic distribution of enlarged folds in 13 cases of Ménétrier's disease and to report six cases of the condition with antral involvement. An attempt will be made to define the process more accurately from the pathologic standpoint.

MATERIAL AND METHOD

Of the cases accessioned at the Armed Forces Institute of Pathology with the diagnosis of "Ménétrier's disease" or "hypertrophic gastritis," 13 cases had adequate roentgenograms and diagnostic pathologic findings and were selected for this study.

The roentgenologic location and distribution of enlarged gastric folds were recorded, with the following topographic designations: fundus, corpus, antrum, greater curvature, and lesser curvature. In some

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cases the enlarged folds appeared to overlie the anterior or posterior walls with little involvement of the curvatures. These were considered "indeterminate" for purposes of curvature analysis.

The pathologic features were independently analyzed from pathologic, operative, and gastroscopic reports, as well as from gross photographs or specimens. Multiple microscopic sections were examined in each case. The required diagnostic criteria included (1) an increase in mucosal thickness from hyperplasia of epithelial cells and (2) formation of obviously enlarged mucosal folds composed of a submucosal core and thickened mucosa (Fig. 1). In addition, particular attention was paid to the cytologic composition of the epithelium; to the amount, type, and distribution of inflammation; and to the appearance of mucosa that was not involved in folded configurations.

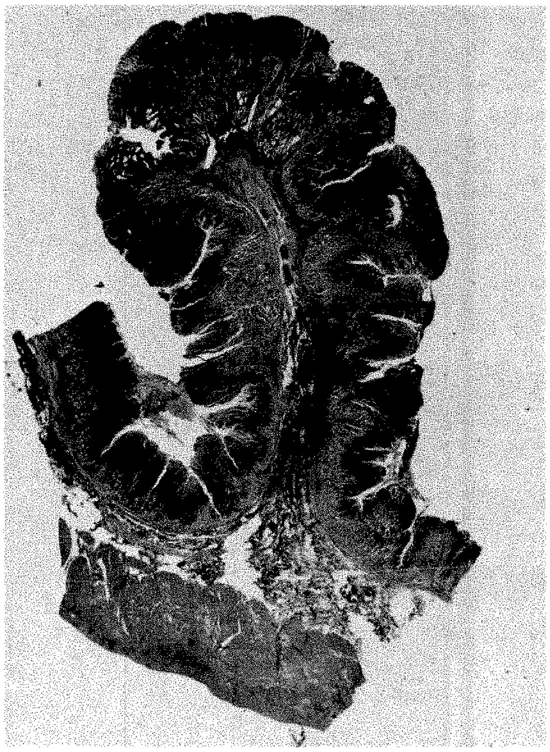

Fig. 1. A typical fold in Ménétrier's disease is composed of thickened mucosa covering a submucosal core. Hematoxylin and eosin (H and E), 4×. (AFIP Neg 74-13228-1.)

Table I

AGE DISTRIBUTION IN 13 CASES OF MÉNÉTRIER'S DISEASE

Age (years)	Number of Cases
<20	1
21–30	2
31–40	2
41–50	3
51–60	3
61–70	1
>70	1
Total	13

RESULTS

Roentgenologic findings. The age distribution of the 13 patients is analyzed in Table 1. The majority of cases (eight of 13) were diagnosed during the fourth, fifth, and sixth decades of life. The ratio of male to female cases was 3 to 1, as was also the ratio of white to black.

The distribution of the enlarged folds by anatomic area is presented in Table II. The corpus, either alone or in combination with another part, was involved more frequently than either the antrum or the fundus. The antrum alone and the fundus alone were

Table II

DISTRIBUTION OF ENLARGED FOLDS BY ANATOMIC PART IN 13 CASES OF MÉNÉTRIER'S DISEASE

Distribution of Folds	Number of Cases	Percent of Cases
Part or combination		
a. Fundus only	1	8
b. Fundus—corpus	0	0
c. Corpus only	6	46
d. Corpus—antrum	3	23
e. Antrum only	1	8
f. Entire stomach	2	15
	13	100
Summation		
Fundus (a+b+f)	3	23
Corpus (b+c+d+f)	11	85
Antrum (d+e+f)	6	46

Table III

DISTRIBUTION OF ENLARGED FOLDS IN RELATION TO CURVATURE IN 13 CASES OF MÉNÉTRIER'S DISEASE

Distribution	Number of Cases	Percent of Cases
Curvature or combination		
a. Greater	4	31
b. Lesser	0	0
c. Both	7	54
d. Indeterminate	2	15
	13	100
Summation		
Greater (a+c)	11	85
Lesser (b+c)	7	54

infrequently affected (once each), but the antrum in combination with the corpus was involved with moderate frequency (five of 13 cases). The summation shows that the corpus was diseased almost twice as often as the antrum, which in turn was involved twice as frequently as the fundus.

The distribution of folds by curvature is shown in Table III. The curvatures in combination were affected more frequently than either greater curvature or lesser curvature alone; in fact, there was no involvement of the lesser curvature alone. The summation indicates that the greater curvature was involved more frequently (85 percent) than the lesser curvature (54 percent).

Table IV

DISTRIBUTION OF FOLDS (ANATOMIC AREA/CURVATURE)

Distribution	Number of Cases	Percent of Cases
Fundus		
GC	1	8
LC	1	8
I	1	8
Corpus		
GC	10	77
LC	6	46
I	1	8
Antrum		
GC	6	46
LC	6	46
I	0	0

GC = Greater curvature.
LC = Lesser curvature.
I = Indeterminate.

The distribution of enlarged folds by anatomic part and curvature is analyzed in Table IV. The obvious finding drawn from this table, a conclusion that is well known, is the high percentage of greater curvature corpus involvement (77 percent). It is notable, however, that the lesser and greater curvatures of the antrum were affected in almost 50 percent of the cases.

Pathologic analysis. The dominant macroscopic finding was the presence of large, firm folds of gastric mucosa (Fig. 2). In three cases the folds occupied an area not larger than 6 cm in greatest dimension. In the remainder the involvement was more extensive, affecting at least one-half of a hemigastrectomy or subtotal gastrectomy specimen. The folds measured up to 1.5 cm in thickness and 3.5 cm in height; intramucosal cysts were often visible. Gross abnormalities of the submucosa, muscularis propria, and serosa were not found. The arrangement of folds was variable and included transverse, oblique, and longitudinal orientations. Mucosa uninvolved by folds was frequently thickened, and the surface

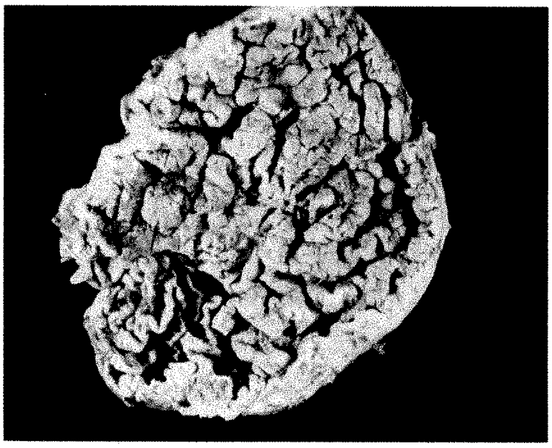

Fig. 2. This resected stomach shows characteristic enlargement of folds. (AFIP Neg 69-11052.)

was often finely lobulated. Ulceration was seldom observed.

Based on our observations and those of previously published reports,[1–3] the salient histologic feature was thickening of the mucosa from elongation of the tubular gastric glands (Fig. 3) and deepening of gastric pits. The individual cells were not enlarged. This alteration seems best categorized as hyperplasia rather than hypertrophy. The cytologic composition of the epithelium often recapitulated what would be normally expected from the anatomic site of the sections. Every case demonstrated cystic dilatation of gastric glands in either the middle third or the deep third of the mucosa, or both. Epithelium was not present beneath the muscularis mucosae. In six cases inflammatory cells were mildly increased in a patchy or diffuse distribution. The core of the folds consisted of edematous or minimally fibrotic submucosa covered by thickened muscularis mucosae. In eight cases long strips of gastric wall adjacent to folds were available for microscopic evaluation. In each case all of the mucosal abnormalities seen in folds were identified (Fig. 4). Microscopic abnormalities of muscularis propria and serosa were not seen.

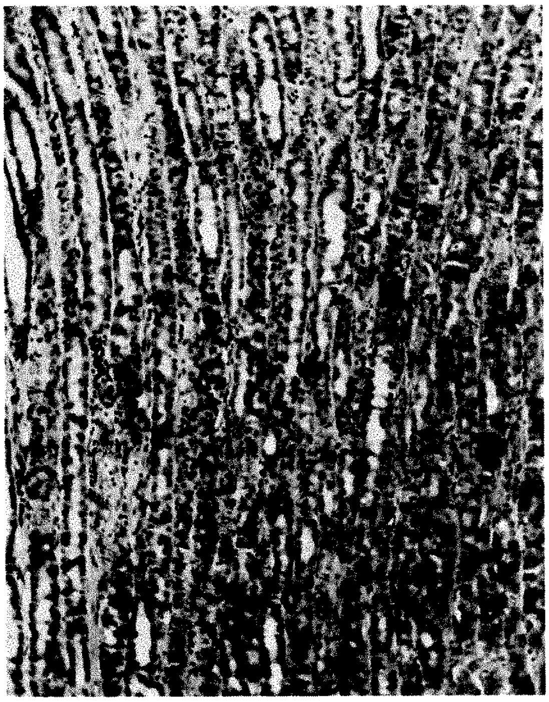

FIG. 3. Elongated tubular glands are composed of a mixture of cells usually seen in normal gastric mucosa. H and E, 90×. (AFIP Neg 74-13227.)

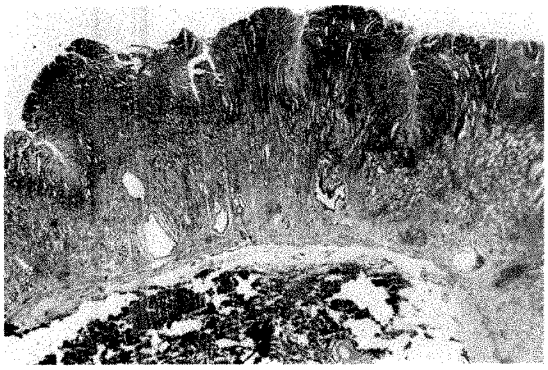

FIG. 4. Mucosa that appeared flat at gross examination shows all the histologic features of Ménétrier's disease when seen microscopically. H and E, 11×. (AFIP Neg 74-13228-2.)

DISCUSSION

Although antral involvement in Ménétrier's disease is mentioned in the literature, it is generally regarded as an unusual manifestation of the condition. Seaman[6] stated that "the antrum is usually spared but may also be involved." Reese *et al.*,[5] in the largest roentgenologic series to date, reported no antral nor lesser curvature involvement.

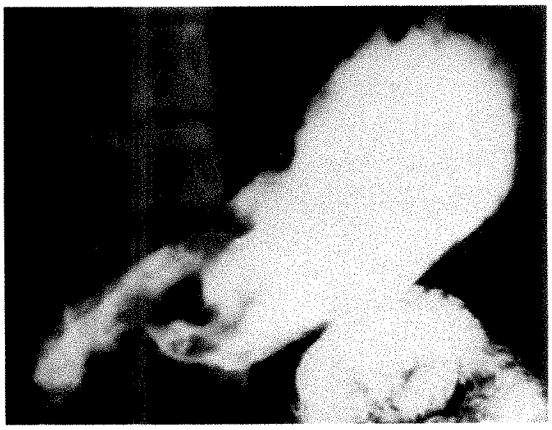

FIG. 5. Isolated antral involvement was seen only once (one of 13 cases). (AFIP Neg 71-4024-1.)

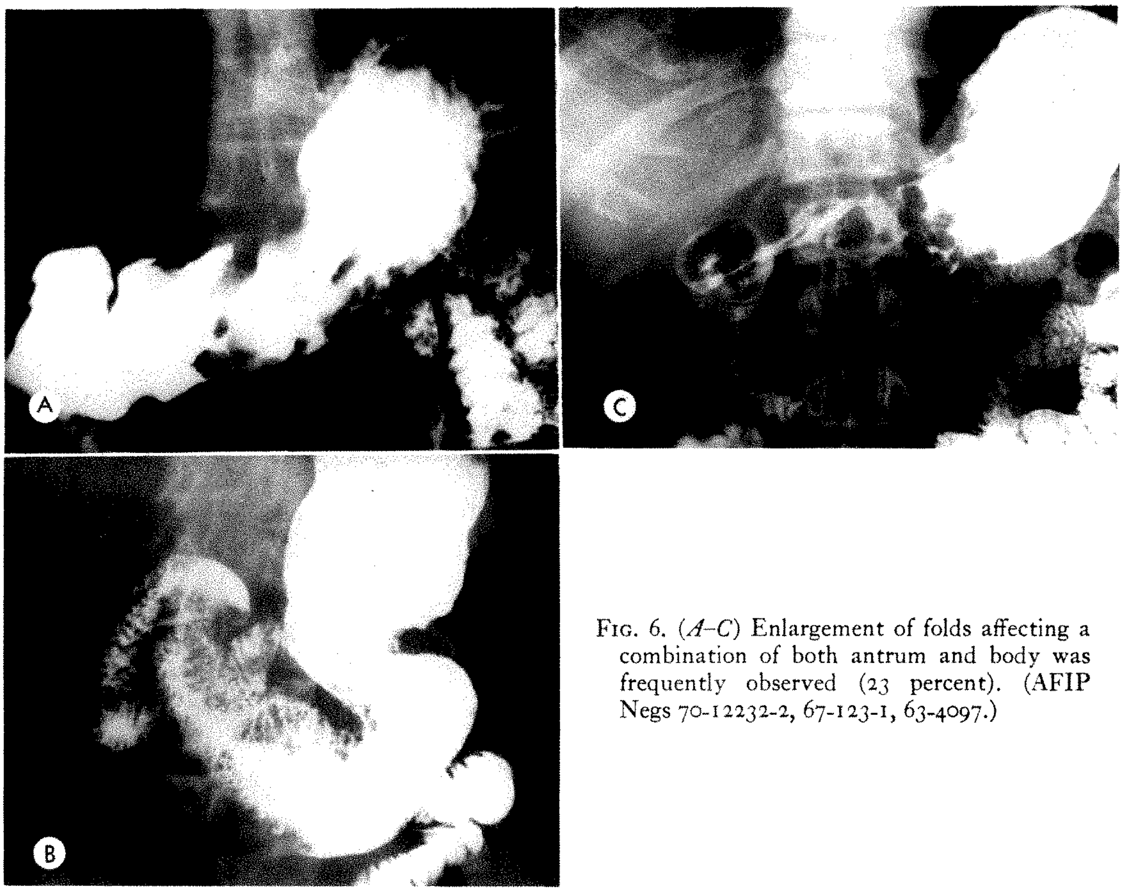

Fig. 6. (*A–C*) Enlargement of folds affecting a combination of both antrum and body was frequently observed (23 percent). (AFIP Negs 70-12232-2, 67-123-1, 63-4097.)

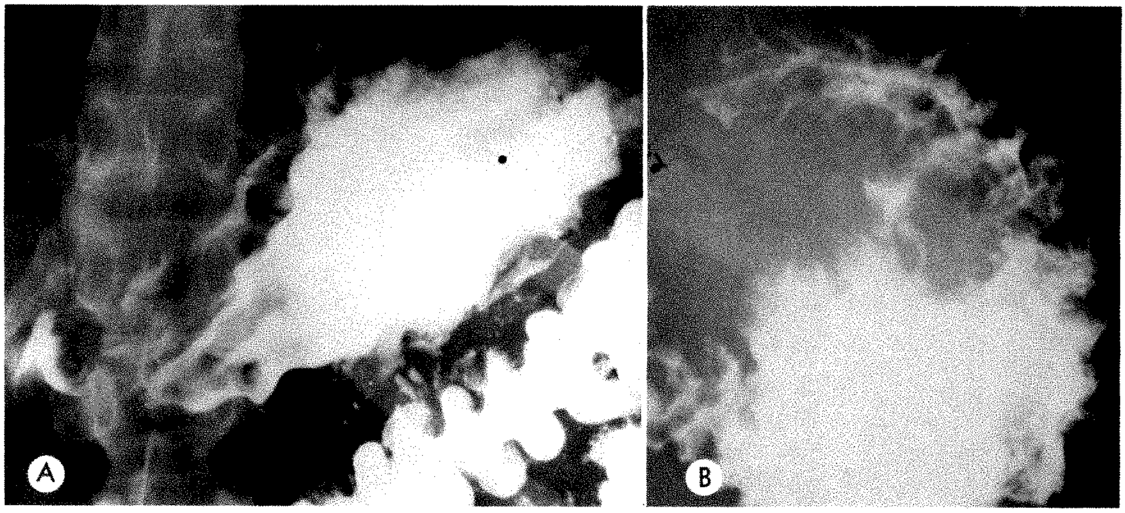

Fig. 7. (*A* and *B*) The entire stomach (including antrum) was involved in two cases (15 percent). (AFIP Negs 69-11190-4, 59-3980.)

The present study substantiates the commonly held view of high frequency of greater curvature corpus fold enlargement. It is obvious, however, that the curvatures of the antrum are also frequently affected (46 percent of cases). Figures 5 through 7 illustrate our findings (six of 13 cases). Antral disease should no longer be considered exceptional, especially when other areas of the stomach are involved. It is important, therefore, to include Ménétrier's disease in the differential diagnosis of enlarged folds affecting any part of the stomach.

The exact nature of this process is not certain. It has not been clear whether the giant folds result from enlargement of pre-existing normal rugae or develop *de novo* as part of the disease process. Multiple sections of mucosa that did not cover thickened folds were available in eight cases. Some of these sections showed the full histologic spectrum of changes present in the mucosa that did cover thickened folds. This suggests that mucosal hyperplasia may precede the formation of folds. Fold formation may simply be a configurational change forced upon the enlarging mucosa by the restrictive limitations of the muscularis propria.

Histologic examination shows that the mucosal thickening is due to additional epithelium. The term "hyperplasia," therefore, seems to describe this process best. Equally obvious from our findings is the frequent lack of inflammation—a point that has not been sufficiently emphasized in the past. In our opinion, the classification of Ménétrier's disease as a variant of gastritis is unwarranted. "Hyperplastic gastropathy" rather than "hypertrophic gastritis" seems to be the most appropriate term.

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NORMAL PANCREAS AND SPLENIC VARIANTS SIMULATING SUPRARENAL AND RENAL TUMORS*

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ABSTRACT:

Two cases of a normal pancreas simulating a renal or suprarenal mass on excretory urography are described. Three cases of unusually shaped spleens and one case of an accessory spleen mimicking renal and suprarenal masses on excretory urography are also presented. The rare entity of splenosis presenting as a renal "mass" on arteriography is also illustrated. The importance of selective arteriography in confirming or establishing the true nature of these pseudotumors which were initially seen on excretory urography is emphasized.

SOFT tissue masses around the left kidney are frequently seen on routine excretory urography. Although tomography is often helpful in clarifying the nature of these masses, arteriography is usually required for definitive diagnosis and exclusion of neoplasm.

We have recently encountered several patients whose urograms showed a mass near the upper pole of the left kidney, which proved to be normal pancreas or variations of the spleen. The purpose of this paper is to familiarize the radiologist with these types of pseudotumors and illustrate their urographic and arteriographic appearance.

To our knowledge, the entity of a normal pancreas presenting as a suprarenal or renal mass on excretory urography has not been previously described.

REPORT OF CASES

A. Normal Pancreas Simulating Renal and Suprarenal Masses.

CASE I. An eight year old white male presented with a three year history of enuresis. Excretory urography showed flattening of the upper pole of the left kidney, but was otherwise normal (Fig. 1*A*). An excretory urogram two years prior to this admission had the same appearance. Urine hydroxy and ketosteroids, aldosterone, vanillylmandelic acid (VMA) and catecholamine levels were normal. A sonogram suggested a left suprarenal mass. Aortography (Fig. 1*B*) and celiac arteriography showed a slightly prominent stain suggesting a mass in the left suprarenal area, but no abnormal vessels were seen. Due to excessive aortic fill during the celiac injection, the arteries feeding the mass could not be definitely determined. Selective renal arteriography confirmed the flattened upper pole of the left kidney, but was otherwise normal (Fig. 1*C*).

At surgery, no abnormal mass was found. The distal body and tail of the pancreas were identified adjacent to the upper pole of the left kidney and were considered the reason for the flattened upper pole.

Comment. The upper pole of the left kidney may be flattened by adrenal tumors and occasionally by variations in the normal spleen.[7] In retrospect, small arteries to the body and tail of the pancreas, arising from the splenic artery, can be seen in the region of the mass on the celiac arteriogram (Fig. 1*D*). However, definitive diagnosis was not made preoperatively since a technically adequate celiac arteriogram or splenic arteriogram was not performed.

CASE II. A 44 year old female was admitted for evaluation of right flank pain and hematuria. Excretory urography with tomography showed a mass arising from the anterior surface of the upper pole of the left kidney (Fig. 2*A*).

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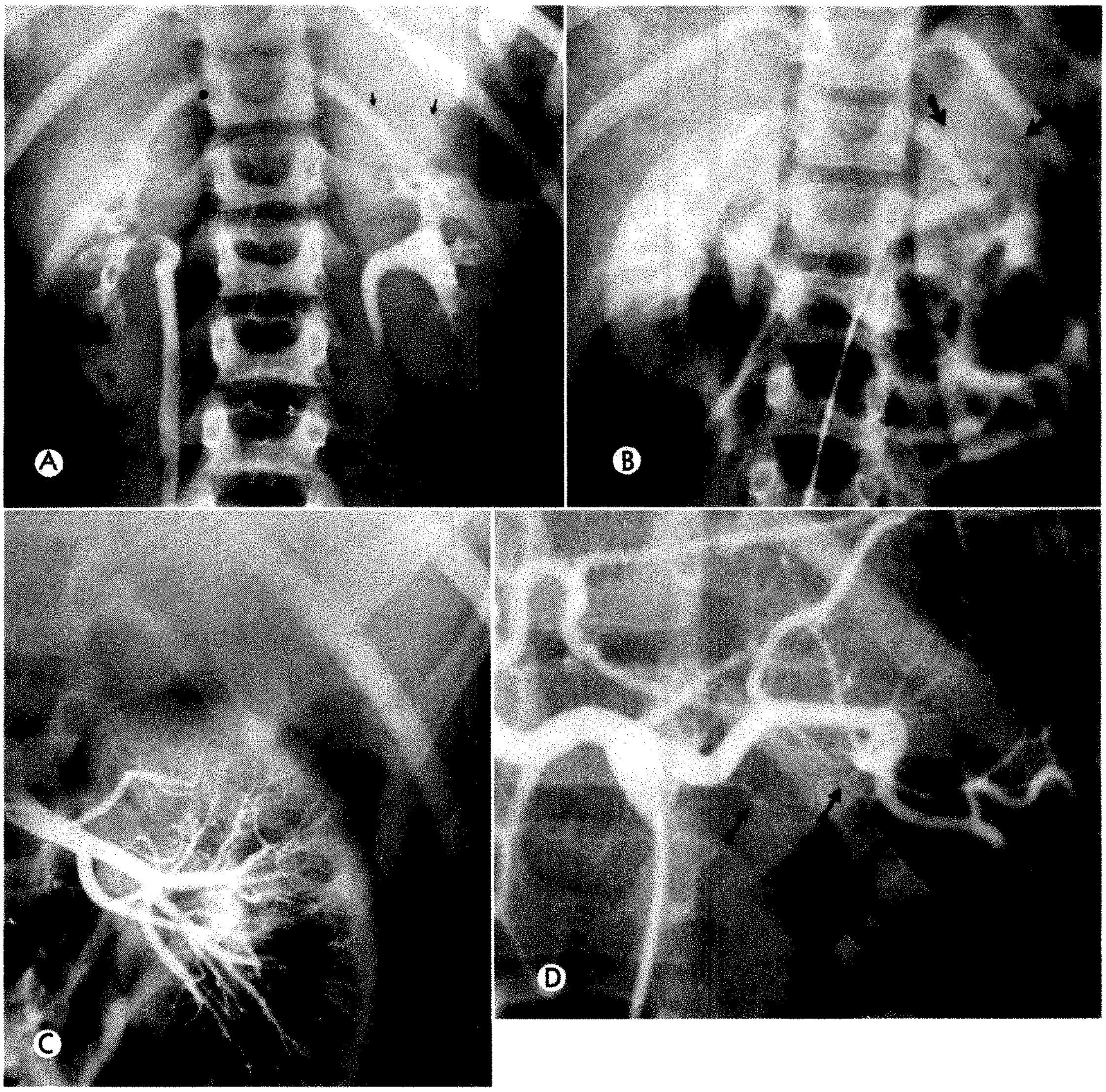

Fig. 1. Case 1. Normal pancreas simulating a suprarenal mass. (*A*) Excretory urogram reveals flattening of the upper pole of left kidney (arrows). (*B*) Abdominal aortogram, late phase. A prominent stain is seen in the left suprarenal area (arrows). Arterial phase (not shown) showed no abnormal vessels in this region. (*C*) Selective left renal arteriogram (1.8× magnification). Flattening of the upper pole is again seen. No abnormal vessels are present. (*D*) Celiac arteriogram demonstrates several normal vessels (arrows) which arise from the splenic artery and supply the body and tail of the pancreas, in the region of the "mass."

Aortography and selective renal arteriography were normal except for pyelonephritic scarring of the lower poles of both kidneys. Celiac arteriography demonstrated that the "mass" seen on the urogram was the tail of the pancreas (Fig. 2*B*). Four days following discharge the patient was readmitted with 80 percent burns and died 17 days later from burn related complications. At autopsy, the kidneys were normal except for some scarring. The adrenal glands, pancreas, and spleen were also normal.

Comment. Abnormal pancreatic masses can simulate intrarenal masses.[4] This case illustrates that the tail of the normal pancreas may also be mistaken for an abnormal mass on excretory urography. In this case, the kidney margin was obliterated by the adjacent pancreas, giving the impression of a renal mass (Fig. 2*A*).

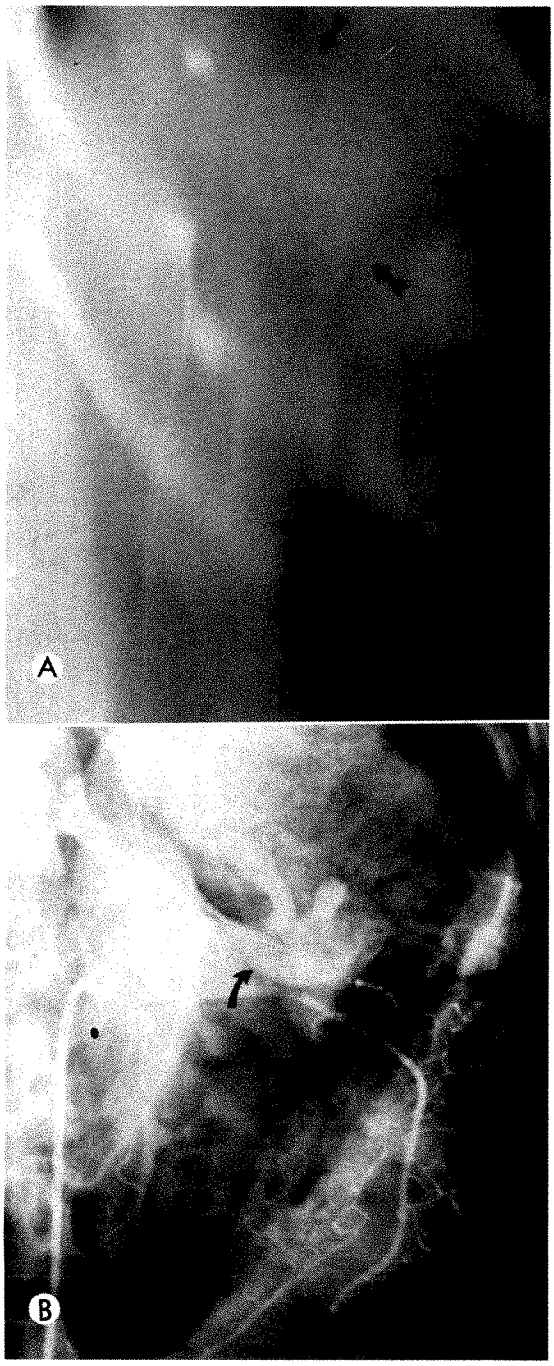

FIG. 2. Case II. Normal pancreas simulating a renal mass. (*A*) Excretory urogram. Laminagram of left kidney (left posterior oblique projection) reveals a mass arising from the anterior surface of the upper pole (arrows). (*B*) Celiac arteriogram (anteroposterior projection), capillary phase. The stain of the pancreatic tail (arrows) corresponds to the "renal mass" seen on the urogram.

B. Splenic Variants Simulating Renal and Suprarenal Masses.

CASE III. A 46 year old female was admitted for abdominal pain radiating to the back. An excretory urogram demonstrated a mass related to the upper pole of the left kidney (Fig. 3*A*). Selective renal arteriography was normal. Celiac arteriography showed this "mass" to be a "tubercle" of the spleen (Fig. 3, *B* and *C*).

Comment. A wide variation in splenic shapes and configurations exists. Michels[8] has distinguished two types of spleens: (1) compact type with narrow hilus and even borders; (2) distributed type with distributed hilus, notched anterior border, a thumb-like lobe at the inferior pole and a tubercle usually at the upper pole, medially. This case illustrates that a tubercle in a distributed type of spleen can mimic a suprarenal tumor.

CASE IV. This 62 year old male with hyperparathyroidism had a history of renal calculi and previous bilateral pyelolithotomies. An excretory urogram showed a small left kidney due to chronic pyelonephritis and postobstructive atrophy, and a mass intimately associated with the left upper pole (Fig. 4*A*). Selective left renal arteriography showed no renal mass (Fig. 4*B*). The "mass" was confirmed by celiac arteriography to be a splenic tubercle (Fig. 4*C*).

Comment. In the presence of chronic atrophic pyelonephritis, the possibility that the "mass" represented residual normal or hypertrophied parenchyma was considered. Selective renal arteriography alone in this case would have been insufficient to make the correct diagnosis and selective celiac arteriography was required to define the true nature of the "mass."

CASE V. A 57 year old male with neurofibromatosis who had previously undergone a left adrenalectomy for a pheochromocytoma, was admitted for evaluation of dysuria. Serial blood pressure and urinary catecholamine determinations were normal. Excretory urography demonstrated a mass adjacent to the upper pole of the left kidney (Fig. 5*A*) which suggested the possibility of local tumor recurrence. Selective celiac arteriography demonstrated a prominent

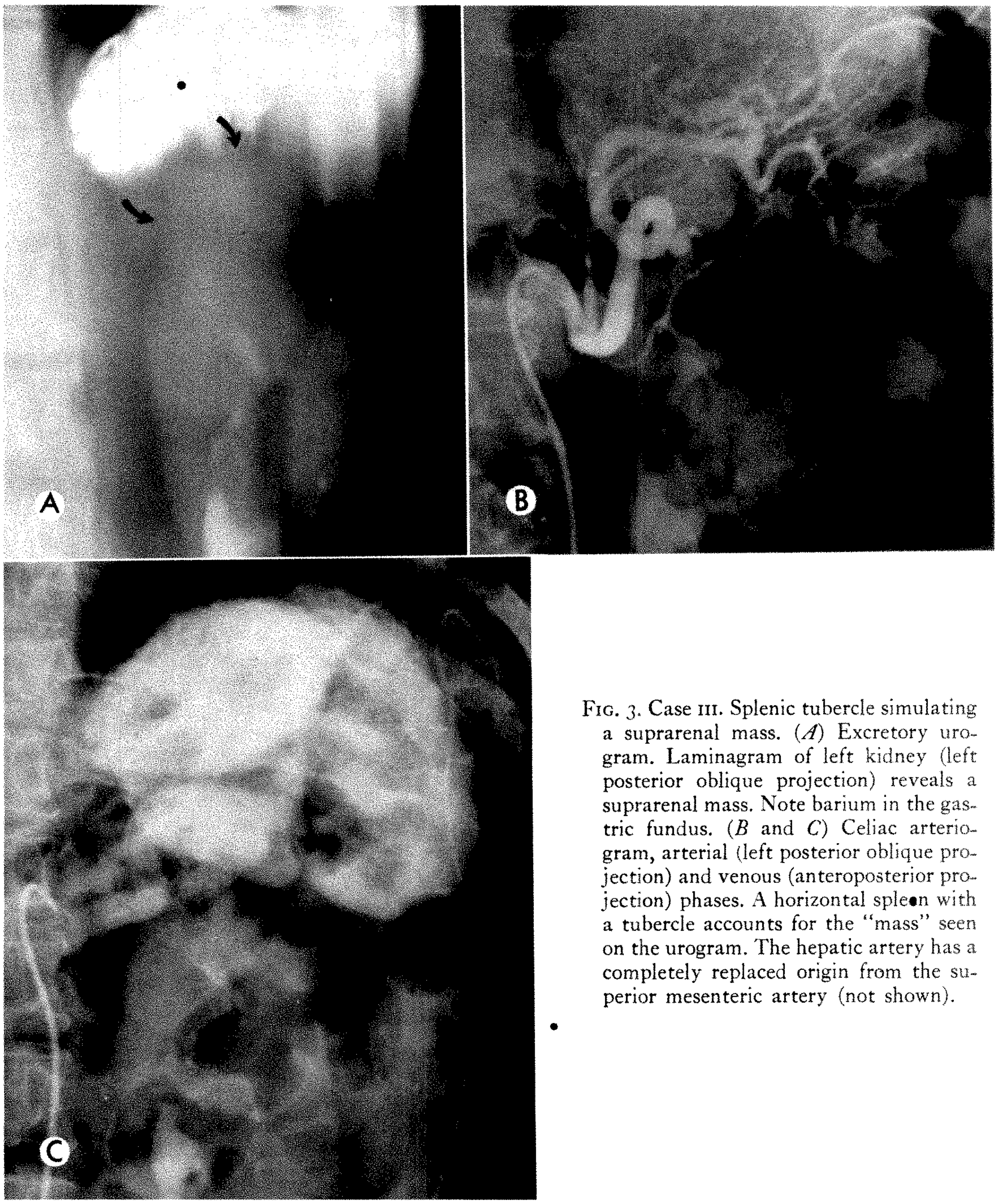

Fig. 3. Case III. Splenic tubercle simulating a suprarenal mass. (*A*) Excretory urogram. Laminagram of left kidney (left posterior oblique projection) reveals a suprarenal mass. Note barium in the gastric fundus. (*B* and *C*) Celiac arteriogram, arterial (left posterior oblique projection) and venous (anteroposterior projection) phases. A horizontal spleen with a tubercle accounts for the "mass" seen on the urogram. The hepatic artery has a completely replaced origin from the superior mesenteric artery (not shown).

lobule of splenic tissue accounting for the "mass" (Fig. 5*B*).

Comment. This is another example of a splenic tubercle associated with the "distributed type" of spleen described by Michels.[8]

Case vi. A 62 year old male was admitted for prostatectomy. Routine excretory urography following surgery showed a mass adjacent to the anterolateral aspect of the midportion of the left kidney (Fig. 6*A*). Although the possibility of an accessory spleen was considered in the differential diagnosis, splenic scan did not con-

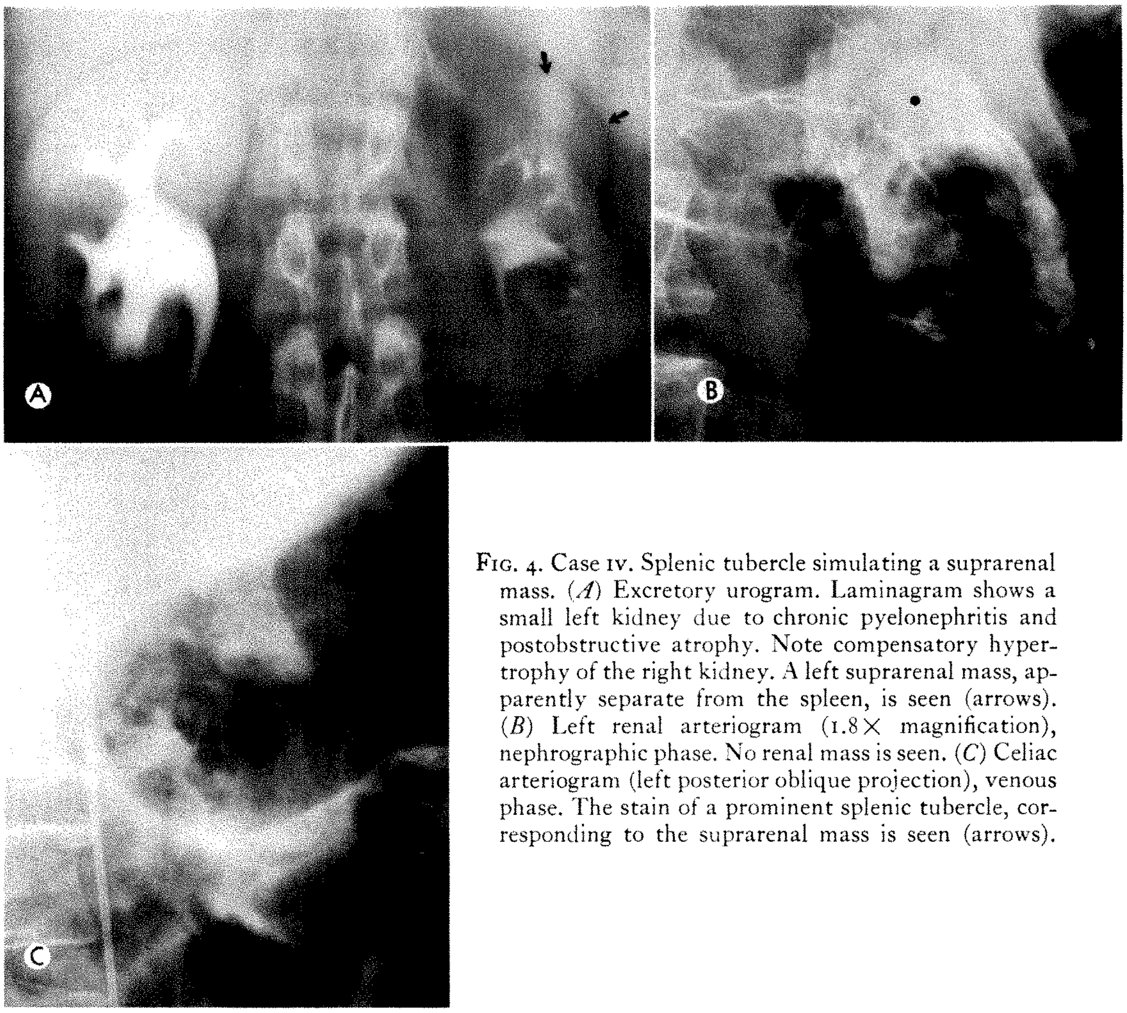

Fig. 4. Case iv. Splenic tubercle simulating a suprarenal mass. (*A*) Excretory urogram. Laminagram shows a small left kidney due to chronic pyelonephritis and postobstructive atrophy. Note compensatory hypertrophy of the right kidney. A left suprarenal mass, apparently separate from the spleen, is seen (arrows). (*B*) Left renal arteriogram (1.8× magnification), nephrographic phase. No renal mass is seen. (*C*) Celiac arteriogram (left posterior oblique projection), venous phase. The stain of a prominent splenic tubercle, corresponding to the suprarenal mass is seen (arrows).

firm this diagnosis. Selective left renal arteriography showed no renal mass (Fig. 6*B*). Celiac arteriography showed multiple accessory spleens near the splenic hilus, and one of these corresponded to the "mass" identified at urography.

Comment. This case is unusual because accessory spleens are usually quite small and rarely present as a mass on excretory urography.[7] At angiography, they may be difficult to differentiate from adrenal, pancreatic, or other retroperitoneal tumors.[2,9] Accessory spleens are most commonly situated in the splenic hilus, but may also be located along the course of the splenic artery as well as in other locations.[2]

Case vii. A 36 year old female, who at age 18 had a splenectomy for idiopathic thrombocytopenia purpura, was admitted for evaluation of hypertension. Selective renal arteriography showed a 3×4 cm hypervascular mass (supplied by a renal capsular artery) arising from the lateral portion of the left kidney, which was considered to be a benign capsular tumor (Fig. 7, *A* and *B*). Subsequent hypertension work-up revealed primary aldosteronism for which a right total adrenalectomy and left subtotal adrenalectomy were performed. The "tumor" attached to the left kidney was excised and was found to be a mass of normal splenic tissue. At operation, multiple other similar splenic nodules were noted in the peritoneum. In view of the past history of splenectomy, these were considered to be the result of splenic rupture at the time of surgery with subsequent "autotransplantation" of splenic tissue (splenosis).

Comment. This case demonstrates an-

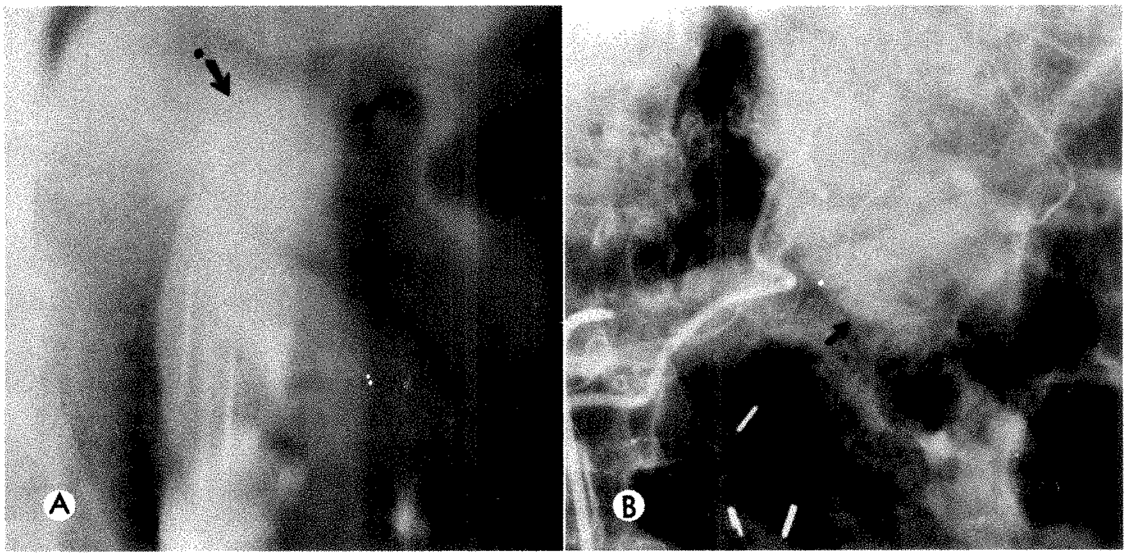

Fig. 5. Case v. Splenic tubercle simulating a suprarenal mass. (*A*) Excretory urogram. Laminagram of left kidney (left posterior oblique projection) shows a suprarenal mass (arrows). (*B*) Celiac arteriogram(1.8 × magnification, anteroposterior projection), venous phase, demonstrates that the "mass" is a prominent splenic tubercle (arrows). Surgical clips are from prior left adrenalectomy for a pheochromocytoma.

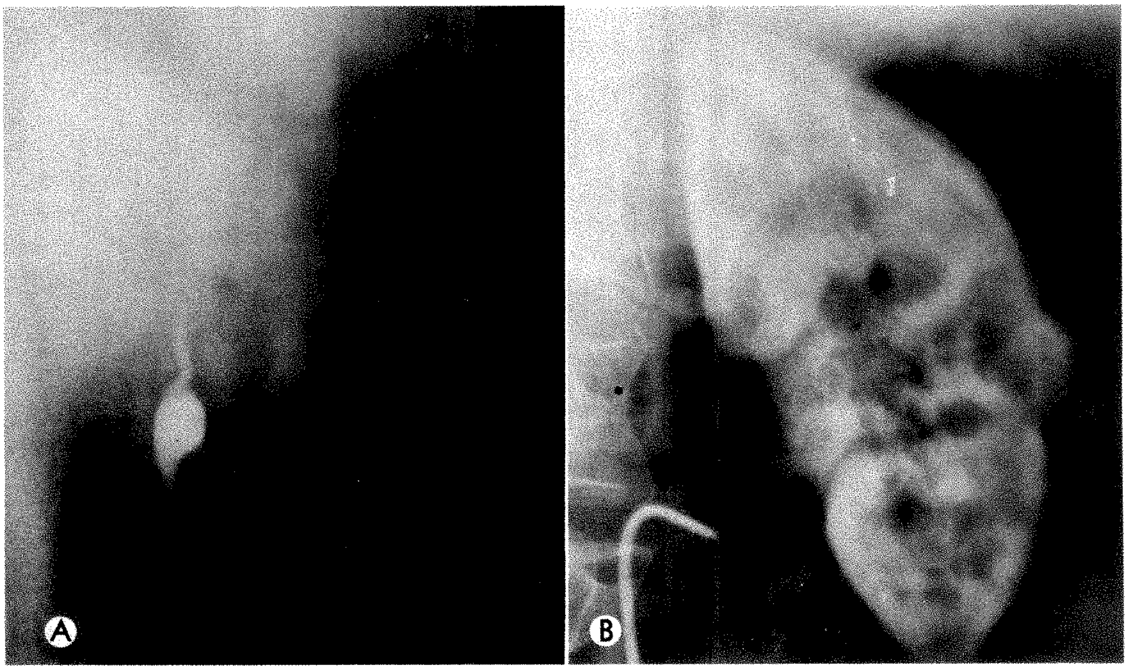

Fig. 6. Case vi. Accessory spleen simulating a pararenal mass. (*A*) Excretory urogram. Laminagram of left kidney (left posterior oblique projection) shows a mass adjacent to the anterolateral aspect of the left kidney (arrows). (*B*) Selective left renal arteriogram (1.8× magnification), nephrographic phase. No renal mass is seen. Celiac arteriogram (now shown) showed multiple accessory spleens, one of which corresponded to the mass seen on the urogram.

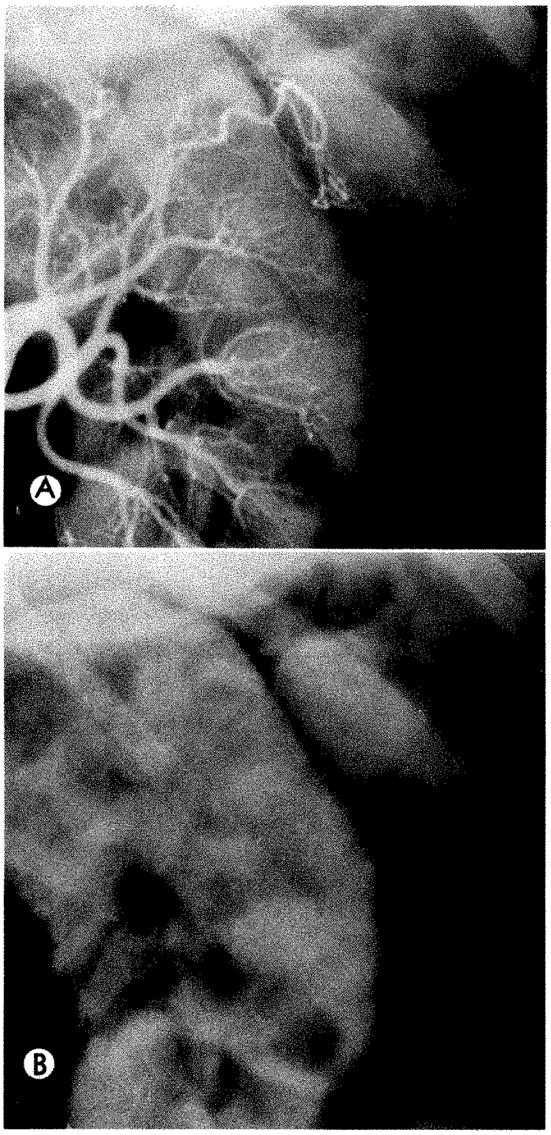

FIG. 7. Case VII. Splenotic tissue simulating a renal mass. (*A*) Selective renal arteriogram (1.8× magnification), arterial phase. A large capsular artery supplying a mass attached to the lateral aspect of the kidney is seen. (*B*) Selective renal arteriogram (1.8× magnification), nephrographic phase. The mass stains diffusely and uniformly (arrows). At surgery, the "mass" proved to be normal splenic tissue.

other extremely rare cause of a renal pseudotumor. The correct preoperative diagnosis of splenosis is rarely made and, as this case illustrates, is often only an incidental finding.[1] If splenosis is suspected, a splenic scan is useful to document the presence of the splenotic tissue preoperatively.[6]

DISCUSSION

Variations in the contour and position of the spleen simulating renal and suprarenal masses have been previously reported by Madayag *et al.*[7] Rarely, a pancreatic pseudocyst[4] or an adrenal neoplasm[10] appears as a mass so intimately related to the kidney on excretory urography that it simulates an intrarenal mass. Accessory spleens, particularly when they enlarge after splenectomy, may closely mimic pararenal[2] or adrenal masses.[9]

An understanding of the close anatomic relationship between the pancreas and left kidney,[11] as well as a realization that wide variations of pancreatic shape and configuration exist,[3] help to explain our cases of normal pancreas simulating renal and pararenal masses on excretory urography. Anatomically, the body of the pancreas extends transversely over the center or upper aspect of the left kidney and only Gerota's fascia and perinephric fat separate the pancreas from kidney itself.[4,5]

Arteriography plays a pivotal role in establishing the true nature of these pseudotumors. Aortography and selective renal arteriography are often insufficient to reach the correct diagnosis. Selective celiac arteriography and, in some cases, splenic or dorsal pancreatic arteriograms may be required to fully explain the "mass" seen at excretory urography. The fact that arteriography helped us reach the correct diagnosis in most of our cases should not negate the role of splenic scanning in delineating an unusually shaped spleen,[7] accessory spleen,[2] or splenotic tissue.[6] Confirmation of a presumptive angiographic diagnosis of an accessory spleen is another use of the nuclear procedure.[2]

Needless operations have been performed in the past in the evaluation of pseudotumors around the upper pole of the left kidney. Since excretory urograms are being requested with increased frequency as part of the "routine roentgenographic work-up," it is likely that an increased number of "mass lesions" will be detected. An appreciation of the existence and roentgenographic appearance of the entities we have described might help to prevent unnecessary surgery. The complementary roles of isotopes and arteriography in cases of unusually shaped or accessory spleens, and technically adequate selective arteriograms in cases of normal pancreas, are crucial for making a correct preoperative diagnosis.

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FAT THICKNESS IN THE NEONATAL SMALL LEFT COLON SYNDROME*

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ABSTRACT:

Increased subcutaneous fat thickness in a neonate with lack of normal stooling should suggest the diagnosis of the neonatal small left colon syndrome rather than Hirschsprung's disease.

DAVIS *et al.*[1] recently reported 20 neonates with clinical evidence of gastrointestinal obstruction who had a markedly diminished caliber of the entire descending colon. The presence of ganglion cells in the narrowed colon, although these cells were smaller and more "immature" than in control cases, differentiated this syndrome from Hirschsprung's disease. Eight of their 20 cases were infants of known diabetic mothers (IDM), and five of eleven asymptomatic IDM's had similar findings on barium enema examinations. Since subcutaneous fat thickness is increased in infants of diabetic and gestational diabetic mothers,[3] we decided to determine fat thickness in a series of neonates with the neonatal small left colon syndrome (NSLCS) as well as in a series with Hirschsprung's disease to see if increased fat thickness might provide an additional clue to the presence of the small left colon syndrome even in neonates whose mothers were not known to be diabetic.

MATERIAL AND METHOD

Fifteen neonates with the clinical and roentgenographic findings of the NSLCS according to Davis' criteria and ten neonates with Hirschsprung's disease were included in the study. Fourteen of those with the small left colon syndrome had rectal biopsies, and in all ganglion cells were present. All ten neonates with Hirschsprung's disease had no ganglion cells on rectal biopsies. Two of the ten with Hirschsprung's disease were mongoloid. Each of these 25 neonates had chest or abdomen roentgenograms during the first three days of life from which lower thoracic subcutaneous fat thickness could be determined[3] (Fig. 1; and 2). Charts were reviewed to determine estimated gestational age according to maternal history and physical examination[2] and history of diabetes mellitus in the mother during pregnancy. Gestational age was assessed roentgenographically by extent of tooth mineralization,[5] thoracic spine length,[4] humeral head ossification,[6] and knee ossification,[7] when possible, to confirm the maternal history of gestational age. Fat thickness of each neonate was plotted according to gestational age by maternal history. The appearance of the initial barium enema examination was

Table I

	Fat Thickness Greater than 2 Standard Deviations Above the Mean	Fat Thickness Less than 2 Standard Deviations Above the Mean
Neonatal small left colon syndrome	10	5
Hirschsprung's disease	0	10

$x^2 = 8.50$
$p < .01$

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compared between the two groups. When postevacuation films were obtained following the barium enema examinations, results were recorded.

RESULTS

Fat thickness was increased in ten of the 15 neonates with the NSLCS to more than two standard deviations above the mean for gestational age (Fig. 2). Four of these ten were not known to be infants of diabetic mothers. Fat thickness of the ten neonates with Hirschsprung's disease was within plus or minus two standard deviations of the mean for gestational age in every case. The difference between the two groups was statistically significant (Table 1).

Six of the ten with Hirschsprung's disease had a narrowed distal colonic segment compared to the proximal colon on their initial barium enema examination, but none had an area of disproportion occurring at the splenic flexure to suggest that they had the small left colon syndrome. Postevacuation films 24 hours after the barium enema examination were obtained in six Hirschsprung's neonates and six with the NSLCS. Four of the six with Hirschsprung's disease had significant residual barium at 24 hours, but two evacuated completely. Neither of these two had roentgenographic or clinical evidence of enterocolitis. Five of the six with NSLCS evacuated barium completely by 24 hours. One required 48 hours to evacuate completely.

DISCUSSION

Fat thickness was increased in two-thirds of neonates with the NSLCS in this study, whereas it was within the normal range in all neonates with Hirschsprung's disease. Measurement of fat thickness can be easily performed on anteroposterior abdomen roentgenograms obtained during the barium enema examination. Increased fat thickness should provide an additional diagnostic clue to the presence of the NSLCS as well as the presence of gesta-

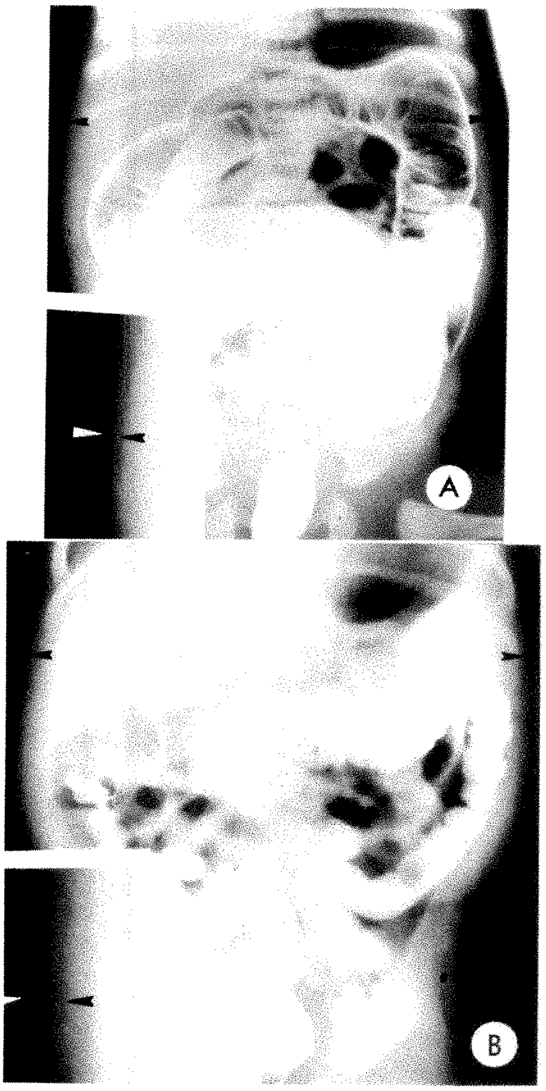

FIG. 1. (*A*) Barium enema examination of a term neonate with Hirschsprung's disease. Persistent narrowing of the distal rectosigmoid colon was present. Fat thickness was measured at the arrowheads. Insert is a magnified photograph of right upper abdomen subcutaneous tissues. (*B*) The entire left colon was narrowed in this neonate without a maternal history of diabetes mellitus. Gestational age was the same as that of the newborn infant in *A*. Insert is a photograph at the same magnification as the insert in *A*, and the fat thickness is double that of the neonate in *A*. A diagnosis of neonatal small left colon syndrome was made, and ganglion cells were present on rectal biopsy.

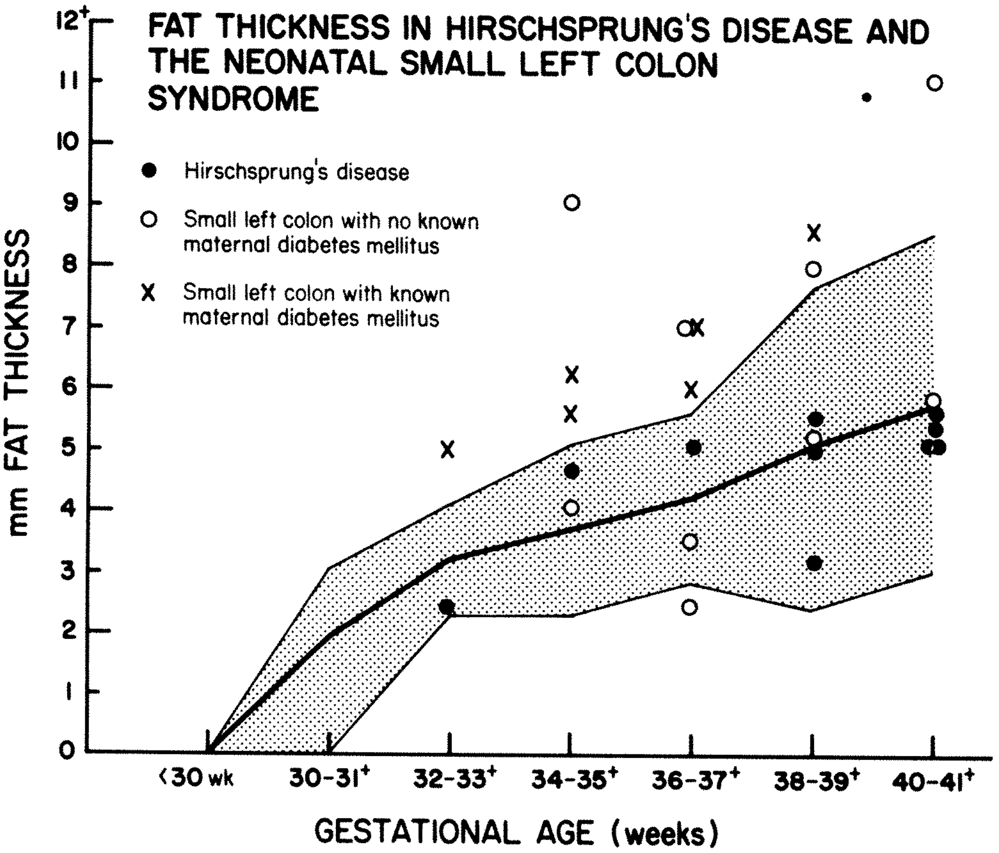

Fig. 2. Note that fat thickness is increased in two-thirds of patients with the small left colon syndrome, whereas neonates with Hirschsprung's disease have normal fat thickness for gestational maturity.

tional diabetes in the mother.[3] If the neonate has a narrowed colon from splenic flexure to rectum and increased fat thickness, the diagnosis is almost certainly NSLCS, since none of the ten neonates in this study with Hirschsprung's disease had a uniformly narrowed entire descending colon. The extent of retention of barium on 24 hour postevacuation films is not too reliable in the diagnosis of Hirschsprung's disease, since two of six neonates with Hirschsprung's disease evacuated barium completely by 24 hours. The small left colon syndrome undoubtedly will be diagnosed more frequently than Hirschsprung's disease in neonates, since five cases of small left colon syndrome have been diagnosed during the last six months and six cases of Hirschsprung's disease were diagnosed during the last five years at the C. S. Mott Children's Hospital.

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RHABDOMYOSARCOMA IN THE PEDIATRIC AGE GROUP*

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ABSTRACT:

Forty-five consecutive cases of pediatric rhabdomyosarcoma were studied as to age at onset, histological type, primary site, stage of disease when first seen, method of treatment, and survival. It appears that rhabdomyosarcoma is a relatively radiosensitive tumor which can be controlled locally with radiation alone or in combination with surgery to excise the bulk of the tumor mass. On the other hand, chemotherapy must necessarily play a major role in treatment since most cases are first seen in the late stages of the disease. Close cooperation among a wide range of specialists, such as the pediatrician, radiation therapist, pediatric oncologist, pathologist, and surgeon is essential to accomplish a maximum therapeutic effect in the unfortunate children who develop this relatively rare but aggressive tumor.

IN this retrospective study, the records of all 45 patients with rhabdomyosarcoma in the pediatric age group who were seen at Indiana University Medical Center from May, 1955 through June, 1974 have been reviewed. Each case history is analyzed as to age at onset, histological type, primary site, stage of disease when first seen, method of treatment, and survival. Of the 45 patients seen, only 41 patients were eligible for a minimum of 18 months tumor-free survival.

INCIDENCE

Fortunately, rhabdomyosarcoma is relatively rare in the general pediatric population, but it represents 18 percent of all pediatric solid tumors and accounts for ten percent of all cancers seen in childhood.[9] In our Center, rhabdomyosarcoma is the second most frequently seen pediatric solid tumor. The age at the time of diagnosis encompassed the entire pediatric age range; the disease was seen from the newborn period to the age of 16 years, with a median age of seven years. Seven patients (16 percent) were seen under the age of one year; the largest number (35 percent) were in the one to five year age group (Table 1).

HISTOLOGY AND PRIMARY SITE

Histological evaluation revealed tumors of the embryonal type in 29 patients (64.5 percent), the alveolar type in five patients (eleven percent), the pleomorphic type in two patients (4.4 percent), and unspecified rhabdomyosarcoma in nine patients (20.1 percent). These histological groupings are similar to those in other studies.

The genitourinary system was the primary site of involvement in 15 patients (33 percent). In twleve patients (27 percent) the primary sites were in the head and neck, and in seven patients (16 percent) the primary sites were in the trunk,

TABLE I

RHABDOMYOSARCOMA IN THE PEDIATRIC AGE GROUP

Age Distribution	Patients	Percent
Under 1 year	7	16
1 to 5 years	16	35
5 to 10 years	9	20
10 to 15 years	13	29
Total	45	100

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‡ Director, Clinical Radiation Therapy Service.

Table II

PRIMARY SITE AND HISTOLOGY

Primary Site	No. of Patients	Percent	Embryonal	Cell Type Alveolar	Pleomorphic	Unspecified
Head and Neck						
Orbit	4	9	4	—	—	—
Other	8	18	6	1	—	1
Trunk	7	16	5	2	—	—
Genitourinary	15	33	10*	—	—	5
Extremities	11	24	4	2	2	3
Totals	45	100	29	5	2	9

* Four patients were classified as sarcoma botryoides.

including the thorax and the abdominal cavity, but excluding the genitourinary system. Interestingly, the primary sites in the trunk included one case in which the heart was felt to be the organ of origin and another in which the trachea was listed as the primary site. In the remainder of the cases, eleven patients (24 percent), the disease originated in an extremity (Table II).

Table III

RHABDOMYOSARCOMA—INTERGROUP PROTOCOL GROUPING

(In this system, the grouping is decided upon by the surgeon in the operating room and later confirmed by the pathologist and pediatrician.)

Group I	A.	Localized disease completely resected, confined to muscle or organ of origin
	B.	Localized disease completely resected, contiguous involvement, infiltration outside the muscle or organ of origin
Group II	A.	Grossly resected tumor with microscopic residual disease but no evidence of regional lymph node involvement
	B.	Regional lymph nodes involved but all disease completely removed
	C.	Regional lymph nodes involved, grossly resected but evidence of microscopic residual
Group III	A.	Incomplete resection or biopsy with gross residual disease
Group IV	A.	Distant metastatic disease present at onset

CLINICAL EVALUATION AND SURVIVAL BY STAGE GROUPINGS

Before entering the rhabdomyosarcoma study group, each patient had an individualized clinical work-up which routinely included a history and physical examination, chest roentgenogram, complete blood count, platelet count, urinalysis, and liver function tests. Bone marrow aspirations, skeletal surveys, liver scans, bone scans, lumbar punctures, and specialized roentgenographic studies, *i.e.*, lung tomograms, arteriograms, etc., were done as indicated, depending upon the site of the primary lesion, the extent of disease, and the opinion of the attending pediatrician primarily responsible for the management of the case.

Whenever possible, our cases were staged retrospectively, using the grouping system recommended by the Intergroup Rhabdo-

Table IV

RHABDOMYOSARCOMA GROUPING OF 45 PATIENTS

Group	No of Patients	Percent
I	6	13
II	4	9
III	12	27
IV	15	33
Unstaged	8	18
Total	45	100

Table V

RHABDOMYOSARCOMA SURVIVAL BY GROUPING (ELIGIBLE FOR 18 MO. FOLLOW-UP)

Group	No. of Patients	18 Months Survival Free of Disease	Percent Survival
I	5	5	100
II	4	3	75
III	11	1	9
IV	13	0	0
Unstaged	8	0	0
Total	41	9	22

myosarcoma Protocol Committee[4] (Table III).

According to this system, the majority of our patients was seen in the late stage of the disease (Table IV). More than half of our cases were in Group III and IV, a factor which dramatically affects prognosis and ultimate survival rate. Sutow[9] has reported that patients with extensive disease have zero percent of a five year survival rate and a median survival of only nine months.

Ten (22 percent) of the 45 patients were seen in Stages I and II and 90 percent of the ten are alive and free of disease, eight for at least 18 months. Of the 35 patients who

Table VI

RHABDOMYOSARCOMA BY PRIMARY SITE, HISTOLOGICAL TYPE, GROUPINGS, METHOD OF TREATMENT AND SURVIVAL TIME

Patients' Initials	Primary	Histology	Group	Method of Treatment	Survival and Free of Disease
(1) E.B.	Forearm	Embryonal	I	Amputation	6 yr., 6 mo.
(2) E.R.	Lower extremity	Embryonal	I	Amputation and Chemotherapy (3 drugs) prophylactically	2 yr.
(3) A.L.	Right buttock	Embryonal	I	Surgical resection	6 yr., 6 mo.
(4) B.G.	Prostate	Embryonal (Sarcoma Botryoides)	II	Preoperative irradiation 3,000 r/3 wk. Prostatectomy, cystectomy, urethrectomy, and postoperative irradiation 2,000 r/2 wk. Co^{60}	4 yr., 10 mo.
(5) H.D.	Cervix	Embryonal (Sarcoma Botryoides)	II	Hysterectomy and postoperative irradiation. Co^{60} abdomen strip 2,500 r/7 wk. and actinomycin-D prophylactically	3 yr.
(6) C.H.B.	Right thigh	Embryonal	III	Surgical excision. 6,000 r/6 wk. postoperative irradiation Prophylactic Chemotherapy (3 drugs)	1 yr., 6 mo.
(7) Y.K.	Anterior abdominal wall	Embryonal	I	Surgical resection and chemotherapy (cytoxan). No radiation	1 yr., 6 mo.
(8) L.M.	Right testis	Embryonal	II	Surgical resection Co^{60} 5,000 r/5 wk. Chemotherapy (3 drugs)	1 yr., 6 mo.
(9) S.A.	Left thigh	Embryonal	I	Surgical resection. Co^{60} 3,600 r/4 wk. Chemotherapy (3 drugs)	2 yr.

were first seen with advanced disease (Groups III and IV), only six survived, two of whom are alive more than 18 months with disease after treatment; three of them are not eligible and only one still remains free of disease (see Table V). All of these patients were in Group III.

Survival by Primary Site, Histological Type, and Method of Treatment

The nine of our original 41 patients who are alive and have been free of disease for at least 18 months are listed in Table VI as to primary site, histological type, grouping, method of treatment, and length of survival. Even though no firm conclusions can be reached on the basis of so few cases, certain observations can be made.

Only those patients with a histologic diagnosis of the embryonal type of rhabdomyosarcoma survived. There were no disease-free survivors in the alveolar or pleomorphic types. The primary site did not appear to influence the survival rate. All four patients with orbital rhabdomyosarcoma had advanced disease when first seen, and while local control was achieved with irradiation in three of the patients and surgery and local irradiation in the fourth, all four succumbed to the disease from distant metastases despite aggressive chemotherapy.

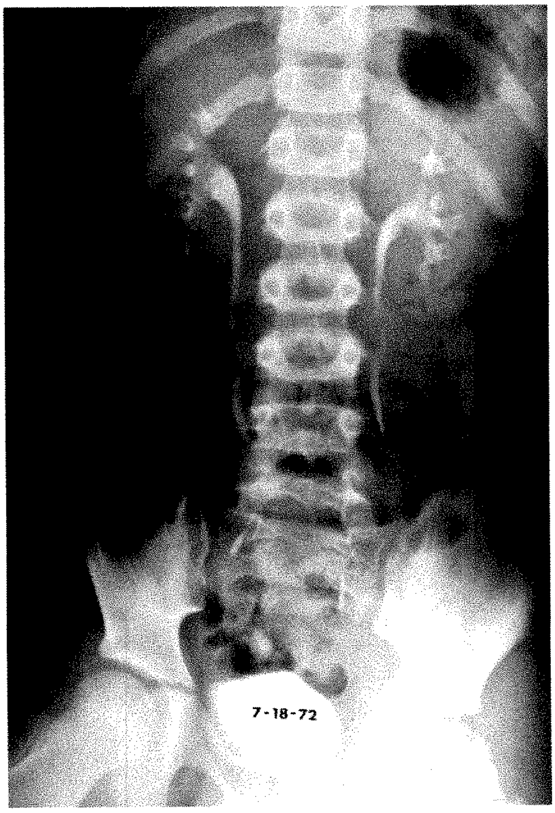

Fig. 1. Intravenous urogram showing the bladder displaced from the left side of the pelvis.

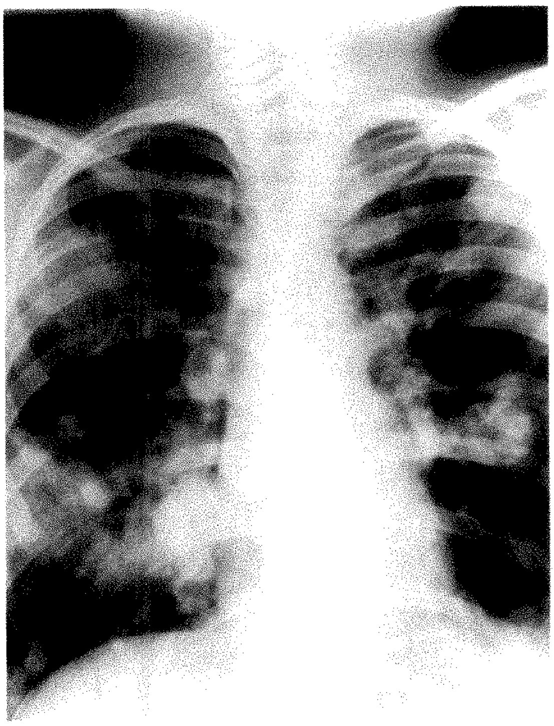

Fig. 2. Examination of the chest on July 17, 1972, showing numerous metastases.

In regard to the treatment modality, surgery was the principal method used in all of our survivors. Two patients received surgery alone, and the rest of the cases received supplemental therapy.

The following case represents the remarkable regression that can occur with appropriate radiation therapy.

REPORT OF A CASE

Case I. J.B., a nine year old white male, was admitted on July 17, 1972 with a history of change in bowel habits and a left inguinal mass.

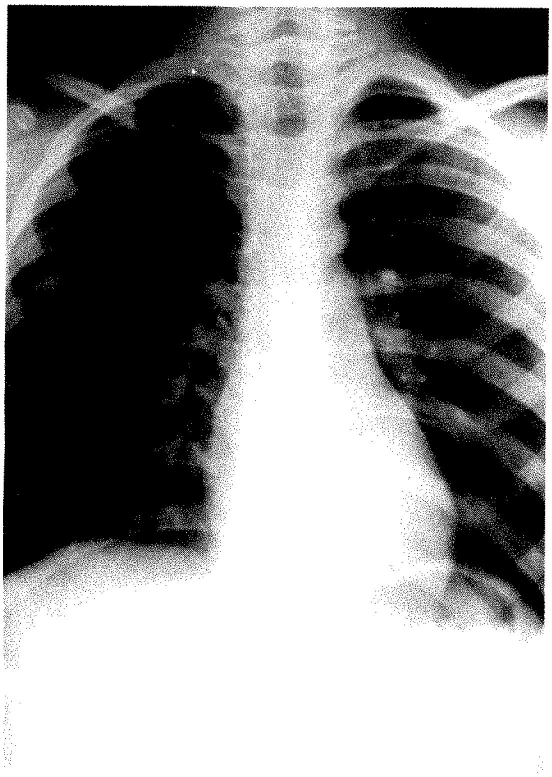

Fig. 3. Examination of the chest on November 28, 1972 showing complete disappearance of the metastases.

Physical examination revealed a well-developed, well-nourished nine year old male in good general health. A node measuring 1.5 cm in diameter was palpable in the left supraclavicular fossa. The abdomen was free of any masses, and a recent incisional scar was present in the left inguinal area. An intravenous pyelogram revealed the bladder to be displaced from the left (Fig. 1). The chest roentgenogram showed multiple nodules in both lung fields (Fig. 2). Histological review of the removed specimen from the left inguinal area revealed an embryonal rhabdomyosarcoma. A bone aspiration was also positive for tumor cells.

The patient was then started on Vincristine, Actinomycin-D, Cytoxon, and Adriamycin according to treatment protocol and was also started on radiation therapy to both lungs and pelvis. He received Cobalt^{60} irradiation to a midline tumor dose of 1,800 rads in three weeks to both lungs and 5,000 rads midline tumor dose in five weeks to the entire pelvis. He tolerated the treatment well and a chest roentgenogram taken four months later, November 28, 1972, (Fig. 3) revealed both lungs completely clear of disease. A bone marrow aspiration revealed no evidence of disease.

The patient developed chickenpox pneumonia January 7, 1973 (Fig. 4). This cleared gradually and a chest roentgenogram taken 18 months later shows no evidence of disease present (Fig. 5). One month following this last chest roentgenogram, July 15, 1974, chemotherapy was discontinued as the patient was asymptomatic, and complete physical examination including all laboratory studies revealed no evidence of disease. Three months after cessation of chemotherapy, the disease recurred in the pelvis (Fig. 6).

DISCUSSION

The single most important factor for survival in our series was the stage of disease when the patient was first seen. In our Group 1 patients, there are five cases in which the tumor was excised completely and all patients survived. Two patients received no chemotherapy and are alive after six and one-half years; the other three

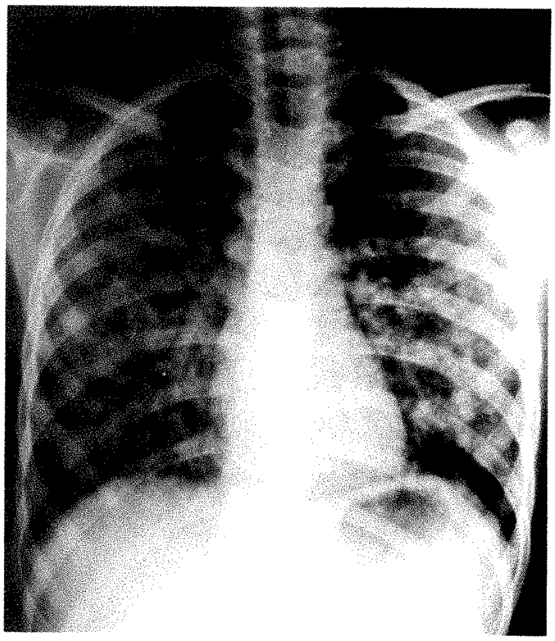

Fig. 4 In January, 1973, the patient developed chickenpox pneumonia.

patients are alive, have been free of disease for 18 months or more, and one received variable doses of chemotherapy. It is difficult to determine whether prophylactic chemotherapy was of any value in the Group I cases.

Diagnosis in the early stages has been unusual. Since most patients will have advanced disease when first seen, a complete evaluation of the patient should be undertaken prior to any treatment as neither radiation, surgery alone, nor any combination of the two can be expected to control widespread metastatic disease. Chemotherapy or another form of systemic therapy must provide the main impetus for future control of this devastating disease; however, chemotherapy may mask persistent disease, and if it is discontinued, metastasis may become evident.

Currently, prior to treatment, all of our patients receive the following evaluation as recommended by the Intergroup Rhabdomyosarcoma Committee Protocol: a history and physical examination, complete blood count, platelet count, urinalysis, bone marrow aspiration, skeletal survey, blood urea nitrogen, creatinine, SGOT, LDH, bilirubin, uric acid, alkaline phosphatase, and liver and bone scans. Superior venocavagrams, arteriograms, and lung tomograms are done as indicated. In addition, brain scans and cerebrospinal fluid examinations are done on all patients with head and neck tumors.

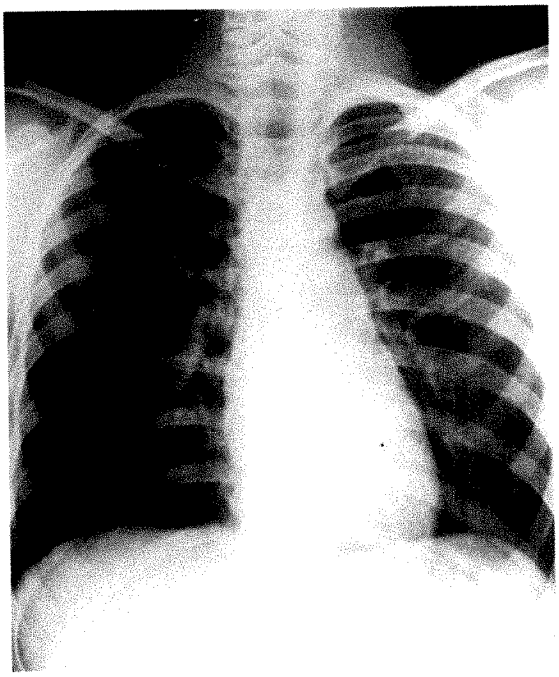

Fig. 5. In July, 1974, there was no evidence of disease in the lungs.

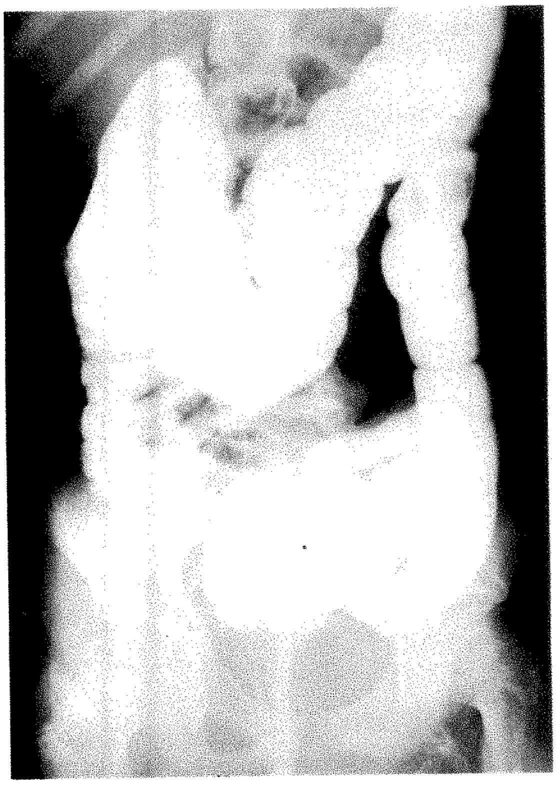

Fig. 6. In October, 1974, three months after cessation of chemotherapy, there was recurrent disease in the pelvis.

As Sagerman *et al.*[7] has pointed out, rhabdomyosarcoma of the orbit is a moderately radiosensitive tumor that can be controlled with high dose irradiation with considerable certainty, as the primary tumor remained controlled in all of their orbital rhabdomyosarcoma patients (15 cases). In our study, high dose radiation proved effective in controlling local disease. The dose varied from 4,500 to 6,000 rads given in four and one-half to six weeks. All radiation was given using supervoltage therapy (Cobalt^{60}) and proper shielding technique with adequate margins for treatment ports to encompass any possible residual disease. The chemotherapy combinations and dosages varied considerably, depending upon the experience of the pediatrician involved in the case. In no case did chemotherapy achieve permanent control in a patient who had known residual disease at the completion of radiation therapy or surgery, or had distant metastases from the outset. Because of the wide variety of chemicals and dosages used, it was felt to be of little value to determine whether these chemicals increased the mean survival rate.

Because of the relatively small number of cases and the wide variation in primary site, grouping, and method of treatment, it is difficult to draw conclusions on the ideal treatment of rhabdomyosarcoma in children.

A few observations and recommendations can be made, however, based upon our study and a review of the literature.[2,6,10]

1. Because many patients will first be seen with advanced metastatic disease, an adequate work-up prior to any definitive therapy must be undertaken to determine accurately the stage (grouping) of the disease.
2. The tumor may be controlled locally with adequate irradiation in 85 percent of the cases.
3. Ninety-two percent of the failures occurred within the first 18 months.

At our center, the following treatment is currently being recommended for patients with children's rhabdomyosarcoma.

a) Group I (local disease completely resected)

The primary tumor should be excised as completely as possible. In head and neck tumors where complete resection is not practical, a biopsy would be sufficient. The gross removal of the tumor should be followed by adequate doses of postoperative irradiation (5,000 to 6,000 rads in five to six weeks) using appropriate radiation therapy technique, equipment, and adequate field sizes to encompass all reasonable extension of disease. Chemotherapy in Group I must be considered optional in that proof is lacking that prophylactic chemotherapy is of value in prolonging life in the early stages of the disease; however, some authors[7,8] have suggested that adjunctive chemotherapy in these groups will possibly increase survival times.

b) Groups II and III (excision of the primary tumor, followed by radiation therapy)

Chemotherapy is recommended as adjunctive therapy as this may increase survival rate.

c) Group IV (widespread metastatic disease)

Local excision of the tumor for diagnosis is recommended. This is to be followed by adequate doses of radiation to the primary site (4,000 to 6,000 rads, depending upon age, in five to six weeks), using proper radiation techniques and equipment. Chemotherapy is necessary in this group if any serious attempts at long term control of these patients are made.

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POSTADRENALECTOMY PITUITARY ADENOMA (NELSON'S SYNDROME) IN CHILDHOOD: CLINICAL AND ROENTGENOLOGIC DETECTION*

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ABSTRACT:

Following total adrenalectomy in Cushing's syndrome associated with adrenal hyperplasia, but not with adrenal adenoma or malignancy, elements of the pituitary may be stimulated to grow rapidly and even aggressively. There is strong evidence to support the idea that there is a pre-existing tumor in many, if not all, of these cases. In some, the tumor may be too small to deform the sella turcica. After adrenalectomy, these patients should be observed carefully and frequently for hyperpigmentation, visual field defects, and sella turcica enlargement.

THE syndrome of pituitary chromophobe adenoma, hyperpigmentation, and marked elevation of plasma adrenocorticotropic hormone after bilateral adrenalectomy for Cushing's syndrome in an adult was first described by Nelson and co-workers in 1958.[18] Since then many other patients have been reported[13,15,16,19,23] at least seven of which were children.[3,12,14,17,26] Because of the rarity of Nelson's syndrome and its apparently increased frequency in association with Cushing's syndrome in childhood,[8,11] and because it is paramount that pediatricians and radiologists recognize the clinical syndrome and detect the pituitary tumor, we are reporting two additional cases. A literature review[3,12,14,17,26] and pertinent features of our cases are contained in Table I.

REPORT OF CASES

Case I. S.S. (SMH #69-40-82). This eight years four months old girl presented in August, 1968 with excessive weight gain over a four year period, but especially in the preceding six months when she gained approximately 10 kg. Past health had been excellent except for scarlet fever, chickenpox, measles, and German measles. There was no significant family history of obesity nor of other medical problems. Physical findings were: round "moon" face; obesity, especially about her trunk with a "buffalo" hump; scant pubic hair and excessive hair on her back; and purplish striae over her lower abdomen and medially on her thighs. Her height was 130.0 cm. (50th percentile) and her weight was 51.1 kg. (97th percentile). Blood pressure was 118/75. Neurologic and ophthalmologic examinations were normal. Roentgenographic findings were: mild enlargement of the sella turcica with intact and symmetrical cortical margins (Fig. 1, *A* and *B*); normal intravenous urogram without evidence of suprarenal masses; advanced skeletal maturation (ten years by Greulich and Pyle standards[9]); and moderate vertebral osteoporosis. Serum electrolytes were: chloride, 101 meq/liter; sodium, 135 meq/l; potassium, 3.7 meq/l; serum calcium, 9.6 mg percent; phosphorus, 3.1 mg percent; and blood glucose, 120 mg percent. Twenty-four hour urinary 17-hydrosteroid determination was 14 mg, and 24 hour urinary 17-ketosteroid determination was 7.6 mg. A dexamethasone suppression test showed that at dose levels initially of 1.5 mg/day there was no suppression but with a dosage of 3.75 mg/day for three days the 17-hydroxysteroid excretion was suppressed to less than 50 percent of control

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TABLE I

CHILDHOOD CUSHING'S SYNDROME AND NELSON'S SYNDROME:
LITERATURE REVIEW AND TWO ADDITIONAL CASES (1974)

Authors		Age	Sex	Sella Turcica Roentgenogram Pre-Adrenalectomy	Adrenal Pathology	Sella Turcica Roentgenogram Adrenalectomy (Duration)		Pituitary Pathology
Montgomery[17]	1959	15	F	Normal	Cortical hyperplasia	Enlarged	(2⅓ yr.)	Chromophobe adenoma
Mannix *et al.*[12]	1960	16	F		*		(4 yr.)	Basophil adenoma
Cassidy[3]	1960	13	F	Normal	Cortical hyperplasia	Enlarged	(3½ yr.)	Chromophobe adenoma
Welbourn *et al.*[26]	1971	11	M	Normal	*	Enlarged	(9 yr.)	*
McArthur *et al.*[14]	1972	7	M	Normal	Cortical hyperplasia	Enlarged	(6 yr.)	*
		12	M	Normal	Cortical hyperplasia	Enlarged	(4 yr.)	*
		14	F	Normal	Cortical hyperplasia	Enlarged	(3 yr.)	Chromophobe adenoma
Young, Lim, Forbes and Bryson (additional cases)	1974	8	F	Borderline enlarged	Cortical hyperplasia	Enlarged	(5 yr.)	Chromophobe adenoma
		12	F	Normal	Normal adrenal tissue†	Enlarged	(2 yr. to 6 yr.)	Basophil adenoma

* Not available.
† A lobular mass adjacent to the left adrenal was highly vascular and was not biopsied.

levels. The iodine^{131} thyroid uptake and thyroid scan were normal.

The patient's findings were consistent with a diagnosis of Cushing's syndrome and in October, 1968 a bilateral adrenalectomy was performed. The combined weights of the adrenals was 10 gm, approximately two times normal for her age. Pathological examination revealed nodular adrenal cortical hyperplasia. She was placed on supportive steroid therapy: cortisone 10 mg q.i.d. and fluorohydrocortisone acetate (Florinef) 0.1 mg daily. Follow-up was at approximately three month intervals and over the next year she did well. Her weight steadily decreased and there was a modest gain in stature. Her sella turcica, as noted on roentgenograms in April, 1969 and September, 1970 was stable in size and appearance.

She was 13 years old in 1973 and despite an advanced skeletal maturation, she had not begun to menstruate and had minimal pubic hair and minimal subareolar nipple development. There was a gradual increase in skin pigmentation, particularly along her digital and palmar creases and postsurgical abdominal scars. In June, 1973 she complained of headaches. These persisted as she experienced progressive difficulty with peripheral vision, and in September, 1973 a right upper temporal quadrantal visual field defect was detected. A plasma adrenocorticotropic hormone (ACTH) assay yielded a value of 1,200 mμ per 100 ml, a

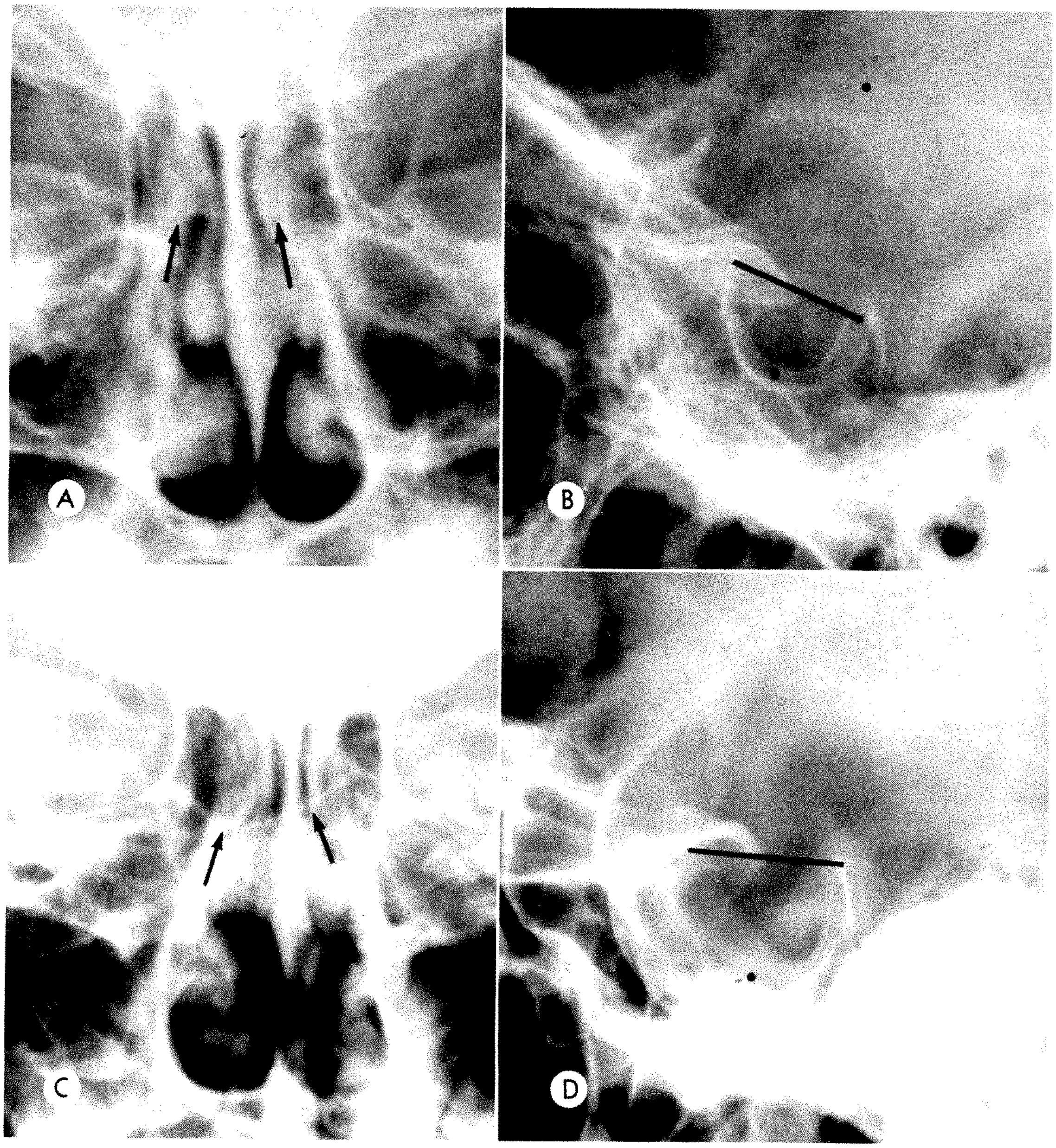

Fig. 1. S.S. (*A*) Anteroposterior view (August, 1968). Note symmetrical floor of sella turcica (arrows). (*B*) Lateral view (August, 1968). Note mild enlargement of sella turcica. Line and dot represent measurement points for area by Silverman technique.[24] (*C*) Anteroposterior view (September, 1973). Note asymmetrical floor (double) and enlargement of sella turcica (arrows). (*D*) Lateral view (September, 1973). Note marked enlargement of sella turcica. Line and dot represent measurement points for area.

markedly elevated level. The sella turcica had enlarged, with right-sided ballooning of its floor without erosion of the dorsum sellae or clinoid processes, consistent with a pituitary tumor (Fig. 1, *C* and *D*). A bilateral carotid angiogram revealed lateral displacement and "opening" of the right carotid siphon and elevation of both anterior cerebral arteries (Fig. 2, *A* and *B*). A pneumoencephalogram revealed superoposterior displacement of the chiasmatic cistern (Fig. 2*C*). Radiation therapy, to arrest tumor growth while preserving production of other pituitary tropic hormones, was elected in preference to surgery. A tumor dose of 4,500

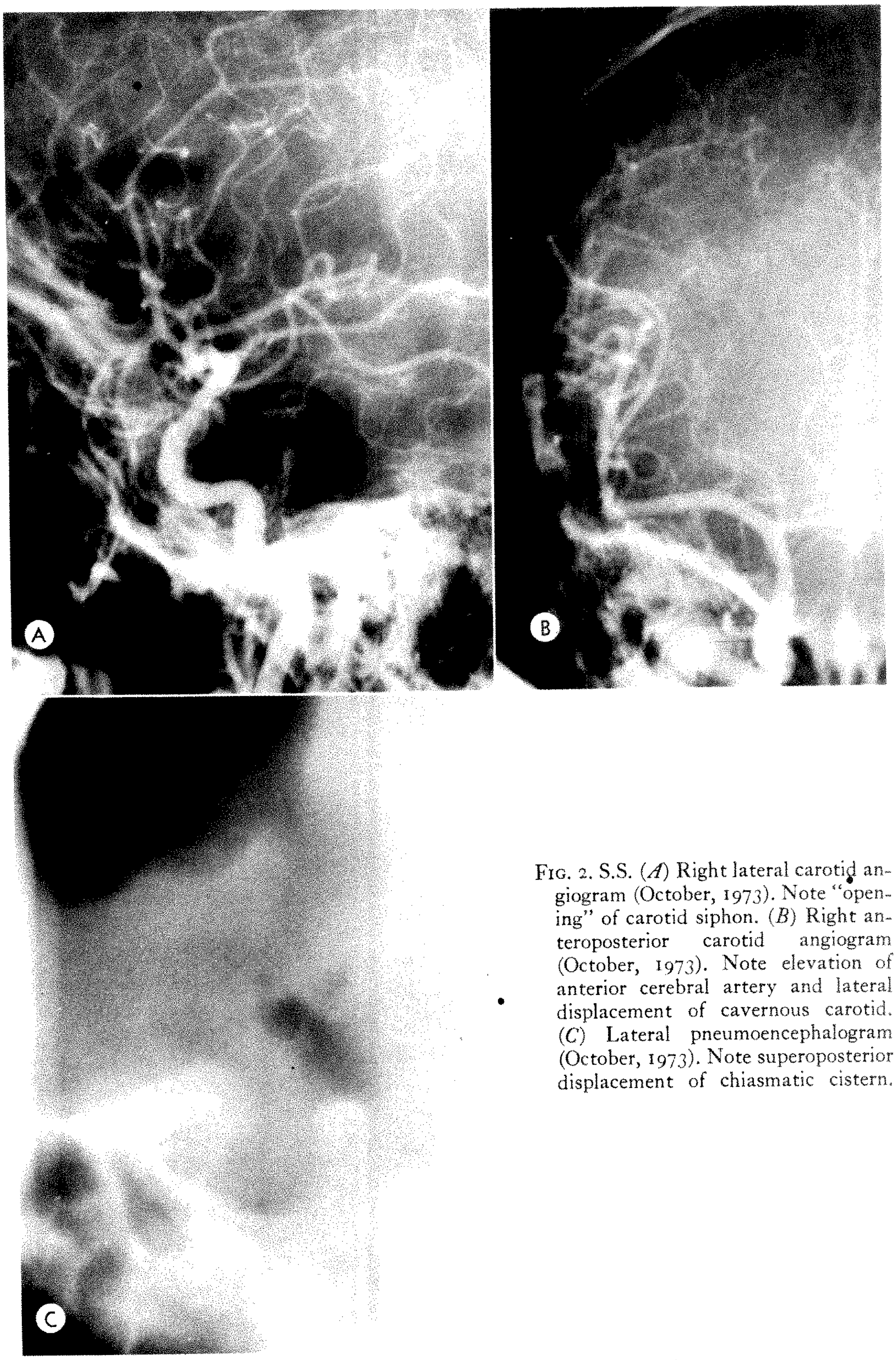

Fig. 2. S.S. (*A*) Right lateral carotid angiogram (October, 1973). Note "opening" of carotid siphon. (*B*) Right anteroposterior carotid angiogram (October, 1973). Note elevation of anterior cerebral artery and lateral displacement of cavernous carotid. (*C*) Lateral pneumoencephalogram (October, 1973). Note superoposterior displacement of chiasmatic cistern.

rads was delivered over a period of six weeks. There was transient symptomatic relief but vision continued to deteriorate and plasma ACTH levels remained in excess of 1,000 mμ per 1,000 ml. In March, 1974 surgical exploration revealed a large pituitary tumor extending superiorly and to the right causing severe compression and flattening of the optic chiasm and the right optic nerve. Partial surgical extirpation was effected to relieve compression. Histologically the tumor was a chromophobe adenoma with areas of necrosis and cystic degeneration.

Subsequently she has been maintained on cortisone, florinef, and thyroid and has done well with a significant weight loss, a slight increase in height, and a decrease in pigmentation. She has occasionally complained of headache and dizziness. Menarche has not occurred and secondary sexual characteristics have been slow to develop. She has had no signs nor symptoms of hypothyroidism or hypocorticism.

Comment. The slight enlargement of her sella turcica at initial presentation supports the concept of a pre-existing anterior pituitary adenoma with relatively rapid increase in size following a bilateral adrenalectomy.

Case 2. L.S.H. (SMH #63-03-97). This twelve and one-half year old girl was admitted in 1966 because of easy bruisability, increasing truncal obesity with "buffalo" hump, cessation of statural growth over a period of four years and no secondary sexual development. On physical examination her height was 131.5 cm (below 3rd percentile) and her weight was 62.5 kg (above 90th percentile). Her face was puffy and plethoric. Her back was hirsute, and reddish striae were noted over her lower abdomen. She was normotensive and her visual fields were normal. Roentgenologic examination revealed minimal osteoporosis, a normal sella turcica (Fig. 3*A*), and normal skeletal maturation. Laboratory determinations were: 24 hour urinary 17-hydroxysteroid determination, 11.8 mg; 24 hour urinary 17-ketosteroid determination, 5.4 mg; dexamethasone suppression test, at a dose level of 1.5 mg every six hours for three days the 17-hydroxysteroid excretion was suppressed to less than 50 percent of control levels. Protein bound iodine estimation and iodine^{131} thyroid uptake were normal. The entire picture was consistent with Cushing's disease. Using an anterior approach a bilateral adrenalectomy was performed in May, 1966. Dissection of friable adrenals of normal size was difficult. Histologically, the tissue was normal.

In the subsequent months her weight decreased from 62.5 kg to 49.8 kg, her dress size of 22½ decreased to 14, and her height increased from 131.5 cm. to 137.5 cm. Within one year, however, she was regaining weight and other clinical signs recurred. Laboratory determinations indicated an exacerbation of Cushing's disease. In January, 1967 re-exploration of the adrenal areas from a posterior approach revealed two glandular structures which had the gross appearance of normal sized adrenals and they were resected. Histologically the tissue was normal adrenal. Adjacent to the left adrenal was a highly vascular lobular mass which was neither biopsied nor removed.

The patient had subsequently been on various replacement steroid regimens and had multiple evaluations in the Strong Memorial Hospital Clinical Research Unit. Although low levels of 17-hydroxysteroid and 17-ketosteroid secretions had been maintained, skull roentgenograms in 1969 revealed that her sella turcica had enlarged and during the period from 1969 to 1973 her palmar creases became more pigmented and her complexion was slightly darker. All of these findings were indicative of pituitary hyperactivity.

In January, 1974 the sella was even more markedly enlarged (Fig. 3*B*) but she had no visual symptoms and visual field examination was within normal limits. On neurological examination she had anisocoria, the pupil of the right eye greater than the left, but no other cranial nerve dysfunction.

She became pregnant while being maintained on cortisone acetate, 10 mg twice daily, and simultaneously complained of progressively severe right frontal cephalgia and occasionally of nausea, but experienced no syncope nor weakness. She was approximately seven months pregnant in August when she was admitted to the hospital. On physical examination she was obese, cushinoid, and hyperpigmented. Her face was puffy, and her smile was asymmetrical, indicating left-sided facial weakness. Ptosis of her right eyelid was present, and her right pupil was dilated (8 mm) and fixed; the left pupil was normal (4 cm). The left pupil showed a consensual response from the right. A "buffalo" hump was present on her back. Skull roentgeno-

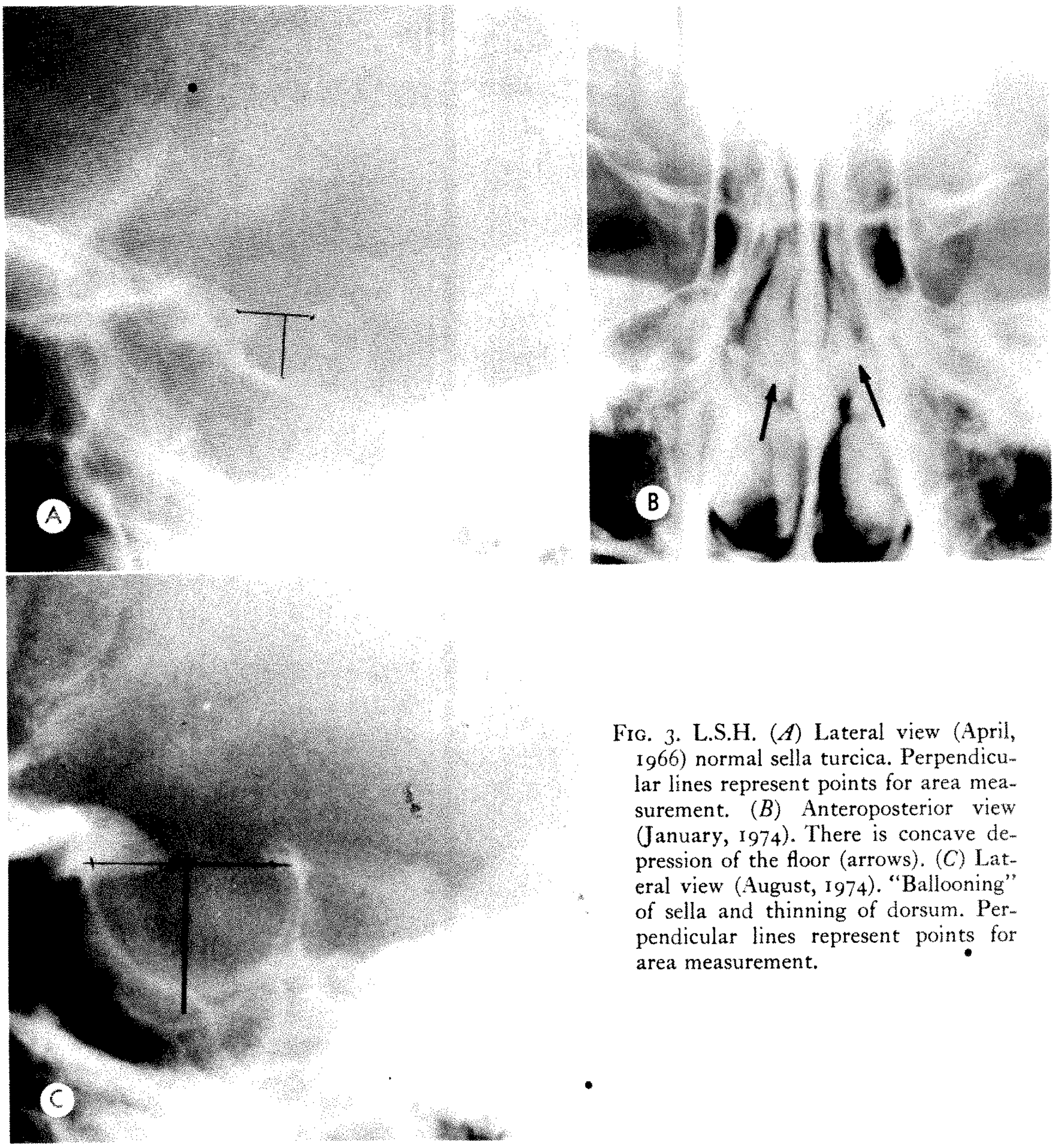

FIG. 3. L.S.H. (*A*) Lateral view (April, 1966) normal sella turcica. Perpendicular lines represent points for area measurement. (*B*) Anteroposterior view (January, 1974). There is concave depression of the floor (arrows). (*C*) Lateral view (August, 1974). "Ballooning" of sella and thinning of dorsum. Perpendicular lines represent points for area measurement.

grams revealed that the sella turcica had enlarged (Fig. 3*C*) in comparison with its appearance in January 1974. Cerebral angiography (Fig. 4, *A* and *B*) and pneumoencephalography confirmed the presence of a large pituitary mass. In September, 1974 she underwent right frontotemporal craniotomy, and approximately 30–40 gm of tumorous tissue were removed from sellar and parasellar areas. On histological examination the tumor was a basophilic adenoma. Her postsurgical endocrine status, initially complicated by diabetes insipidus, was successfully controlled with appropriate hormonal replacement. In mid-October, 1974 at 38 weeks' gestation a healthy 1,780 gm infant girl was delivered by cesarean section. She subsequently developed a staphylococcal abscess of the craniotomy flap and the right temporal lobe which was confirmed by carotid arteriography. Surgical removal of the bone flap and incision and drainage of the temporal lobe abscess were performed, and antibiotic therapy was instituted. After three weeks of prolonged fever and personality disturbances,

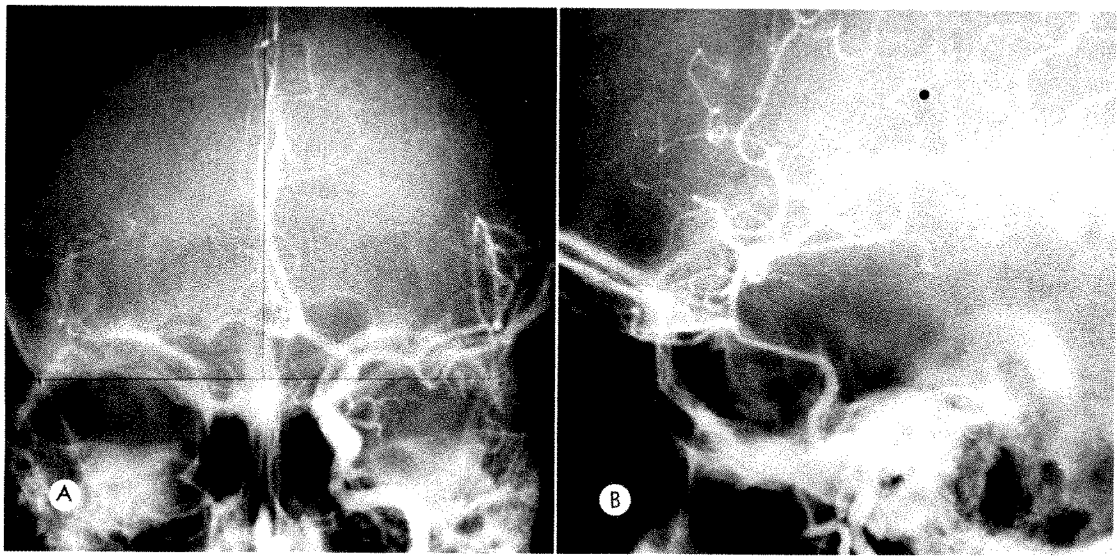

FIG. 4. L.S.H. (*A*) Left cerebral angiogram anteroposterior view (September, 1974). Note elevation of the anterior cerebral artery and lateral displacement of cavernous carotid. (*B*) Left cerebral angiogram lateral view (September, 1974). Note "opening" of carotid siphon.

she gradually stabilized. She was placed on cortisone acetate and synthroid and has done well.

Comment. Although initial laboratory determinations (17-hydrosteroids, 17-ketosteroids, and dexamethasone suppression) were consistent with adrenal hyperplasia, the adrenals, on initial (apparently subtotal) resection and on subsequent resection, were of normal histology. In this case, Cushing's syndrome and the subsequent development of Nelson's syndrome have apparently been on the basis of a basophilic adenoma, too small to cause sellar enlargement at the time of presentation.

DISCUSSION

Childhood predominance. Eberlein and Winter[8] contend that Nelson's syndrome is more likely to occur in children with Cushing's syndrome than in adults. More recently Hopwood and Kenny[11] surveyed the Lawson Wilkins Pediatric Endocrine Society, and the number of childhood post-adrenalectomized Cushing's syndrome cases from respondents totaled 31, eight of which (27 percent) developed Nelson's syndrome (our two cases included). This incidence is higher than the adult incidence of less than ten percent.[21]

Role of the anterior pituitary. The basis for one form of Cushing's syndrome is commonly thought to be increased adrenocortical activity secondary to idiopathic hyperplasia of the adrenal glands. Recognition of Nelson's syndrome has led to renewed attention to the concept that the initiating lesion may be in the anterior pituitary as was originally suggested by Cushing in 1932.[5] Cushing believed that the pituitary lesion was a basophil adenoma which was undetectable by clinical and roentgenologic means. His original report, however, includes three non-basophil pituitary tumors.

In 1965 Rovit and Berry,[22] in a review of the literature concerning Cushing's syndrome associated with non-basophil pituitary tumors, found 50 cases and added five. In approximately 75 percent of these the pituitary tumors were chromophobe adenomas. The chromophobe adenoma is the most common pituitary tumor associated with Cushing's syndrome.

Hypothalamic regulation. It is postulated that the ultimate cause of most ACTH secreting pituitary adenomas resides in the hypothalamus. The adenomas remain under hypothalamic regulation *via* secretion therefrom of corticotropin releasing factor (CRF). Apparently, the target organ hormone in sufficient quantity will suppress the tumor. Since glucocorticoid hormones can also suppress ACTH secretion in patients with bilateral adrenal hyperplasia with and without known pituitary tumor, suppression tests cannot separate these groups of patients. Current evidence suggests that hypersecretion of ACTH by a pituitary basophil adenoma or by a chromophobe adenoma is due to a derangement of the "pituitary" driving mechanism. These interrelationships suggest that the cause of the adrenal hyperplasia is a primary hypothalamic or a mid-brain disturbance rather than a pituitary one. Heinbecker[10] in 1944 noted atrophy of the paraventricular nuclei in certain patients with adrenocortical hyperplasia, but this atrophy, as well as the pituitary hyaline changes described by Crooke[4] in 1935, may be the result rather than the cause of the excess cortisol secreted in bilateral adrenal hyperplasia. Thus, it appears that proof of the primary hypothalamic-limbic-midbrain theory will rest with eventual demonstration of increased CRF levels in the blood or spinal fluid in patients with Cushing's syndrome. Supportive evidence, however, has been the demonstration by Nelson and Sprunt[20] of high levels of plasma ACTH in Cushing's syndrome patients in whom there has been appearance of or rapid enlargement of pituitary tumors after partial or total adrenalectomy.

Roentgenologic detection. The role of roentgenology in the diagnosis of pituitary tumors is well established. Roentgenologic manifestations have been summarized by several authors.[1,2,6,16,25] The findings are revealed by such well established and frequently used procedures as plain skull roentgenography, tomography of the sella turcica, pneumoencephalography, and cerebral angiography. Newer and less often utilized techniques such as isotopic brain scanning, transverse axial computerized tomography, and cavernous sinus venography will undoubtedly play an increasingly significant role.

Plain skull roentgenography including anteroposterior (Fig. 1*C*) or half axial and lateral (Fig. 1*D*) may show enlargement of the sella turcica, "ballooning" or "cupping," with a "double" floor appearance in asymmetric masses. Very large tumors may cause erosion of clinoid processes and dorsum sellae. Measurement of size may be by area on lateral roentgenograms[24] or may be by volume frontal and lateral roentgenograms.[7]

Pneumoencephalography is the examination of choice to reveal size and shape of even minimal suprasellar extensions of tumor, as well as relationships of adjacent structures such as the optic nerves, the optic chiasm, and foramen of Monro. In the presence of larger masses there may be nonfilling of the suprasellar portion of the chiasmatic cistern. Confusion may be caused by overlap of gas in the lateral extension of chiasmatic cistern; however, this may be excluded by laminagraphy. Similarly, retained fluid anterior to the arachnoid membrane of Liliequist may be mistaken for a mass. The posterior border of a suprasellar mass may be well outlined by gas in the interpeduncular cistern but the anterior border is infrequently evident.

Cerebral angiography is utilized especially for excluding a carotid aneurysm, which may not be distinguishable from a pituitary tumor on plain roentgenograms or by pneumoencephalography. The first segment of the anterior cerebral artery (Fig. 4*A*) may be elevated, or there may be straightening and elevation of the supraclinoid portion of the internal carotid artery ("opening of siphon") (Fig. 4*B*). In revealing suprasellar extension, cerebral angiography is approximately one-half as accurate as pneumoencephalography. However, lateral extension of tumor is better demonstrated by angiography, in the form of lateral displacement of the cavernous carotid, the posterior portion of which is normally more medial than the anterior portion. When laterally displaced, the posterior segment is in line with or lateral to the anterior segment, and the cavernous carotid is lateral to the precavernous portion. Lateral extension is most accurately revealed, however, by cavernous sinus venography.

SUMMARY

1. It has been well established that following total adrenalectomy in Cushing's syndrome associated with adrenal hyperplasia, elements of the pituitary may be stimulated to grow rapidly and even aggressively. The fact that approximately one-half of reported cases and our Case I have shown minimal sellar enlargement even before adrenalectomy is evidence in support of pre-existing tumor in many, if not all, cases. In the other one-half of reported cases and our Case II which had normal size and appearance of the sella prior to adrenalectomy, the tumor was probably too small to cause sellar enlargement.

2. Morbid and even mortal consequences may result from the local pressure effects upon the optic pathways and from sustained increased production of ACTH.

3. The predominate pituitary lesion is not basophil adenoma but rather chromophobe adenoma.

4. Nelson's syndrome has occurred secondarily only in those cases in which the adrenal lesion has been hyperplasia and not in those showing adenoma or carcinoma.

5. Because isolated laboratory findings cannot always document a developing or enlarging ACTH secreting pituitary chromophobe adenoma, it is essential that all patients, adrenalectomized because of Cushing's syndrome, have (a) frequent clinical follow-up for the development of or the worsening of hyperpigmentation, (b) visual field examinations at corresponding intervals, and (c) roentgenological monitoring of the sella turcica at close intervals (every six months, or more often if tumor is suspected).

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CHANGING CLINICAL AND ROENTGENOGRAPHIC PATTERNS OF NECROTIZING ENTEROCOLITIS*

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ABSTRACT:

Necrotizing enterocolitis (NEC) occasionally deviates from the classical presentation of the disease. Small bowel dilatation and pneumatosis are frequently present prior to the actual onset of the clinical presentation. Pneumatosis intestinalis, an important diagnostic sign of NEC, is quite variable; it may be present, persist, worsen, or disappear; or at times it may not be present at all. A severe complication of necrotizing enterocolitis is perforation which in 50 percent of the cases presented without obvious free intra-abdominal air. Accumulation of fluid in the abdomen is stressed as strong evidence for perforation and a strong indication for surgery. The varying features indicate that NEC has a clinical spectrum that extends from benign to severe, and recognition of all these variations will lead to better diagnosis and to a better understanding of the disease. The clinical and roentgenologic variations make classification difficult but the variety most likely represents the combination of a great number of susceptible children and a greater recognition of the disease.

NECROTIZING entercolitis (NEC) is a potentially lethal disease with a special predilection for the premature. However, the severity of the disease is quite variable and the incidence and mortality of this disease differ from institution to institution and from area to area. Most published accounts of NEC relate to the more classical clinical and roentgenographic presentations. These include the rapid onset of abdominal distention, acidosis, and bloody diarrhea accompanied by certain roentgenographic findings, particularly intramural intestinal air (pneumatosis). The diagnosis is obvious when all these features are present. However, in some instances the symptoms may be minimal and as a result there are cases that probably remain undiagnosed. It is our intention in this report to present our experience with certain features of NEC that deviate from the usual presentation of the disease. Some of the findings are not unique and have been described by others in one form or another. Nevertheless, better recognition and understanding of these changes will allow for greater appreciation and earlier diagnosis of the disease.

MATERIAL

The findings presented in this paper were derived from a group of 40 cases of necrotizing enterocolitis encountered in a newborn nursery during the past 18 months. The diagnosis was established either by autopsy, surgery, peritoneal tap, or roentgenography when the classic diagnostic features of NEC were apparent. Although 40 cases have been fully diagnosed, the total number of patients with NEC encountered in our institution is probably much larger.

DIAGNOSTIC FEATURES

Disparity between roentgenographic manifestations and clinical time of onset. The diagnosis of NEC is considered when a premature infant presents with the rapid onset of abdominal distention, bloody diarrhea, and often shock. Confirmatory roentgenographic findings of generalized bowel distention, intramural air with or without pneumoperitoneum, and portal venous gas are frequently present. However, this association of clinical and roentgenographic findings does not always occur simultaneously. In fact, in some instances diagnostic roentgenological changes occur hours before the clinical features are manifested. If these features are recognized the diagnosis can be suspected and proper treatment instituted long before the disease is even clinically suspected. In a recent presentation, Siegle *et al.*[7] described the association of small bowel dilatation with either abdominal distention, acidosis, or non-bloody diarrhea as the earliest features of NEC (Fig. 1). This combination of clinical and roentgenographic findings occurred in nine of twelve NEC patients and preceded the actual diagnosis of the disease by four to 48 hours. The underlying pathogenesis for this manifestation is uncertain. However, it is possible that the early ischemic changes that occur in the ileocecal region account for the small bowel dilatation by initiating a localized physiologic obstruction. The ileocecal area is most frequently involved in the early phases of the disease. Selective small bowel distention may not occur, however, if the disease involves other areas of small bowel or colon.

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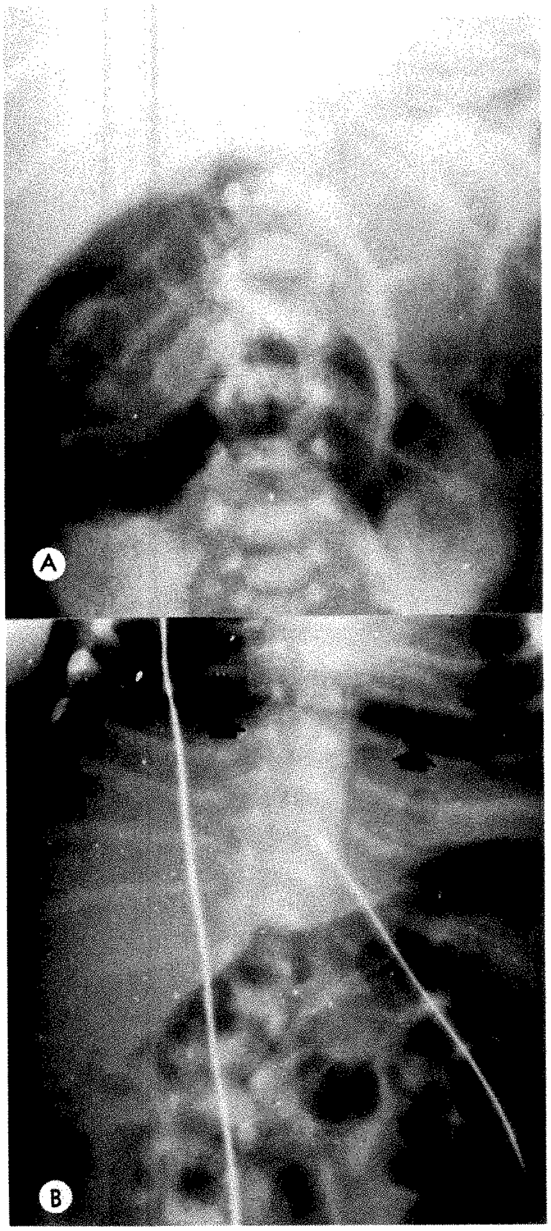

Fig. 1. (*A*) Abdominal roentgenogram in a premature newborn infant reveals markedly dilated small bowel. The infant was distended but relatively asymptomatic. (*B*) The patient was still relatively asymptomatic although free air is now visualized (arrows). Surgery revealed NEC of the ileocecal region.

To our surprise intramural air was also observed in some cases well before the clinical manifestations of the disease were obvious. This may seem paradoxical, since pneumatosis in NEC should follow mucosal destruction. The latter theoretically should be present only when the disease has fully developed. Nevertheless, in one relatively asymptomatic infant air was not only suspected within the wall of the left colon but was easily recognized in the portal venous system (Fig. 2*A*). It required a full 24 hours before the infant developed clinical signs of abdominal distention and acidosis. At this time, gas was diffusely distributed throughout the colon, and the infant died shortly thereafter with a full blown picture of necrotizing enterocolitis (Fig. 2*B*). Pneumatosis of an entire colon was also noted in one patient whose abdomen was examined by x-ray following a bout of vomiting after a normal feeding (Fig. 3*A*). Twenty-four hours later the patient's clinical status and roentgenograms suggested the diagnosis of NEC

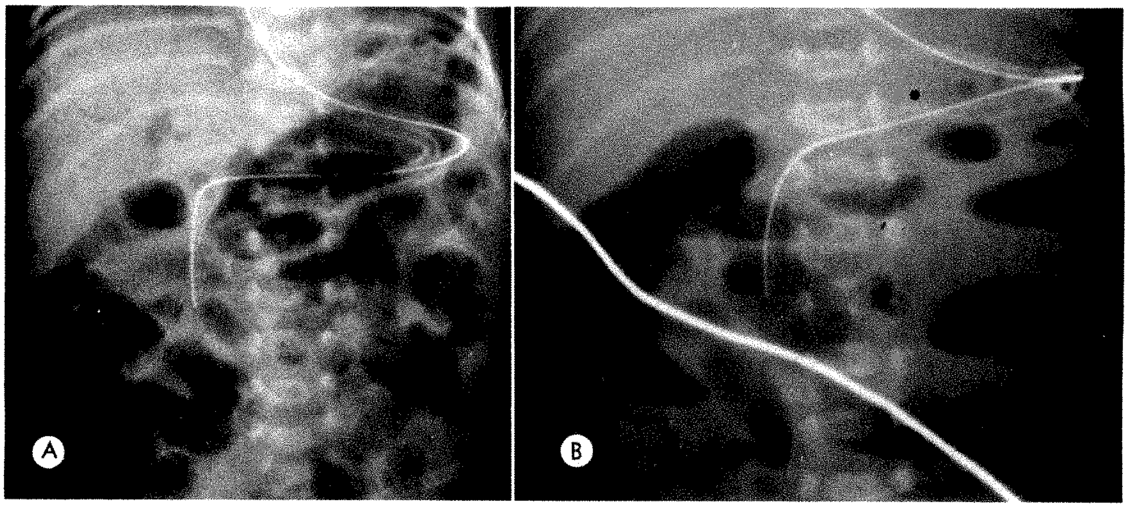

FIG. 2. (*A*) A 1,200 gm asymptomatic infant had a roentgenogram taken at seven days for feeding tube placement. Portal venous gas is evident. There are several lucent streaks in the left mid-abdomen that are thought to represent intramural air. (*B*) Twenty-four hours later abdominal distention associated with lethargy became apparent. There are now prominent lucent streaks of intramural air on the right. Fluid is present in the abdomen as indicated by separation of the bowel loops.

(Fig. 3*B*). This was confirmed by laparotomy. Bell *et al.*[1] also noted pneumatosis as an early finding in the majority of their cases of NEC. The diagnosis in their patients was also suggested by roentgen studies because of the presence of pneumatosis well before any other convincing evidence of the disease was manifested.

Although pneumatosis is an excellent roentgenographic indication of the disease, there are cases of NEC diagnosed at surgery or at autopsy in which intramural air was not demonstrated on the available roentgenograms. Pochachevsky and Kassner[4] noted that only 40 percent of their cases with NEC presented with pneumatosis. Intramural air apparently may appear and disappear rapidly and this accounts

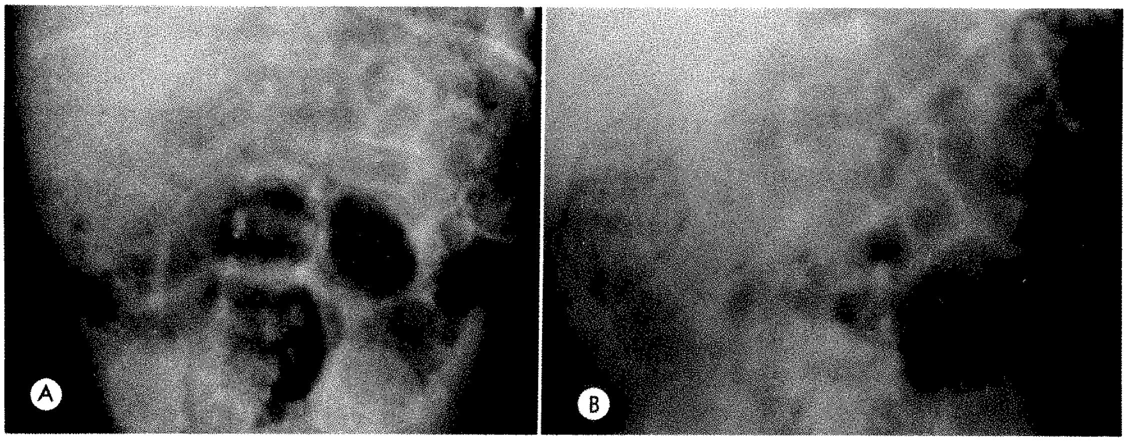

FIG. 3. (*A*) Term infant with roentgenogram taken at 48 hours of age because of vomiting after a normal feeding. There is extensive colonic dilatation with linear pneumatosis along the descending colon. (*B*) Twenty-four hours later the infant developed distention, diarrhea, and acidosis. Extensive intramural air outlining most of the colon was even more obvious.

for the difficulty in correlating pneumatosis with the clinical features in these cases. This was well demonstrated in one case (Fig. 4) in which linear pneumatosis encircled the descending colon but was not present on a roentgenogram exposed 18 hours later and just six hours prior to the infant's death.

Perforation without free air. Bowel perforation is unfortunately a relatively frequent complication of NEC. Without surgical intervention, the mortality incidence is almost 100 percent. Early recognition of bowel perforation is, therefore, imperative if any improvement of these figures is to be made. The diagnosis is facilitated when free air is detected on an abdominal roentgenogram. Small amounts of air may be difficult to visualize and mul-

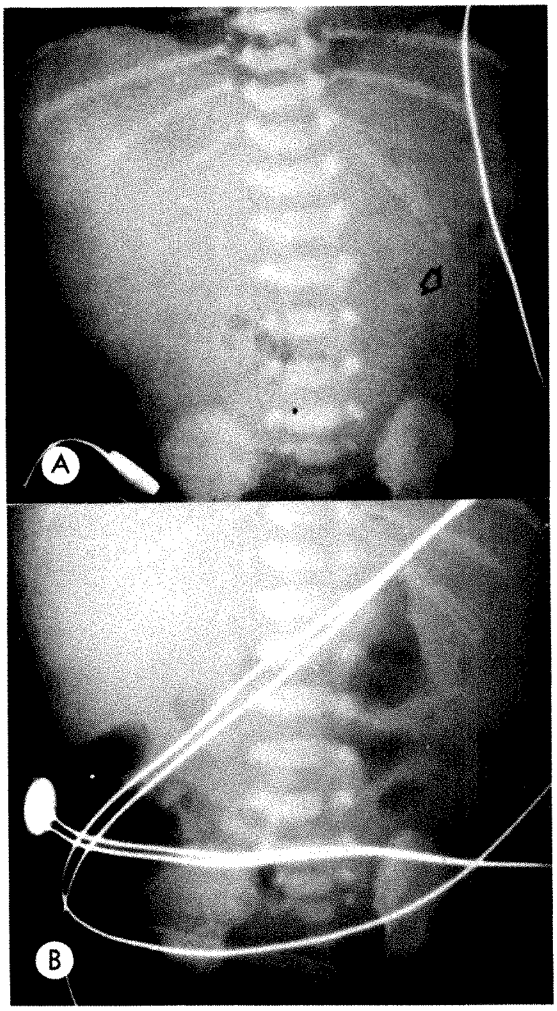

Fig. 4. (*A*) Six day old premature infant with an essentially gasless abdomen and intramural air within the descending colon (arrows). (*B*) Roentgenogram 18 hours later and six hours before death no longer shows pneumatosis. However, intra-abdominal fluid is apparent.

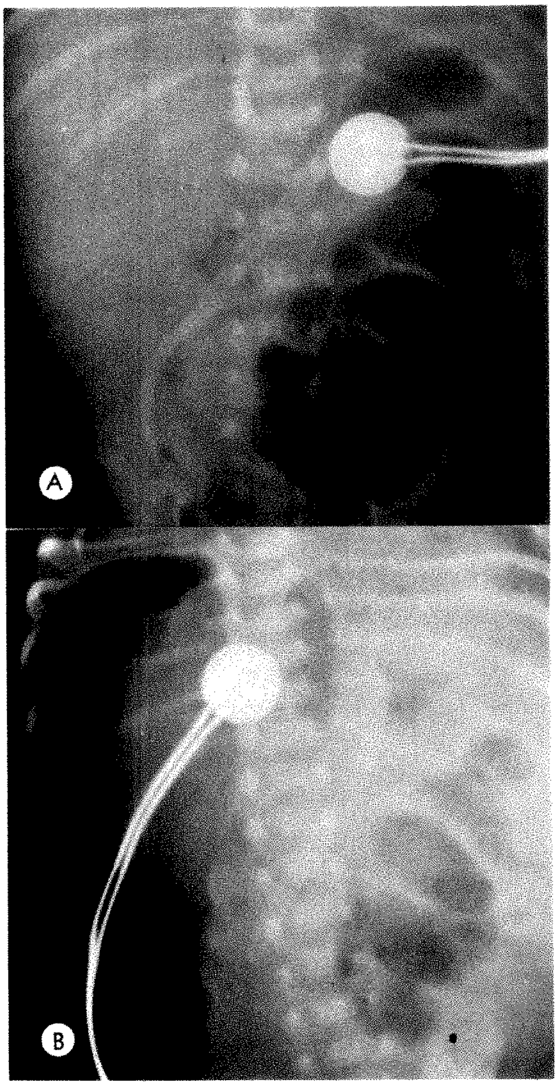

Fig. 5. (*A*) An 8,800 gm infant who developed vomiting and distention at seven days of age. Abdominal roentgenogram reveals only distended loops of small bowel on the left. No colon distention nor pneumatosis is seen. (*B*) Repeat examination three days later demonstrated massive pneumopreperitoneum associated with sepsis. At laparotomy, starting one inch from the ligament of Treitz, twelve inches of perforated and necrotic jejunum were removed.

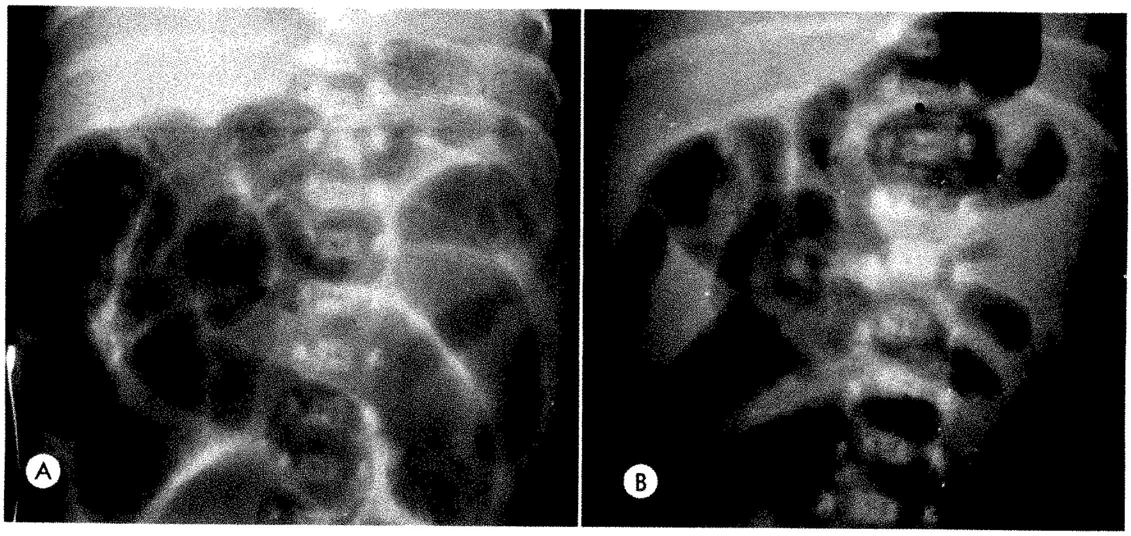

FIG. 6. (*A*) Premature infant who at 15 days of age suddenly developed apnea, acidosis and distention. Abdominal roentgenogram taken within 48 hours reveals marked bowel dilatation and intramural air on the right. (*B*) Forty-eight hours later air is seen in only a few widely spaced loops of small bowel. Peritoneal tap confirmed the presence of purulent peritoneal fluid. Laparotomy two days later revealed massive small and large bowel necrosis with multiple sites of perforation.

tiple projections should be utilized to demonstrate it. However, in our series only 50 percent of the patients with proved perforation demonstrated free air on the abdominal roentgenograms (Fig. 5). Perforation with ensuing peritonitis occurs, therefore, in a high percentage of cases without obvious roentgenographic evidence of pneumoperitoneum. The site of perforation is quickly sealed over by ad-

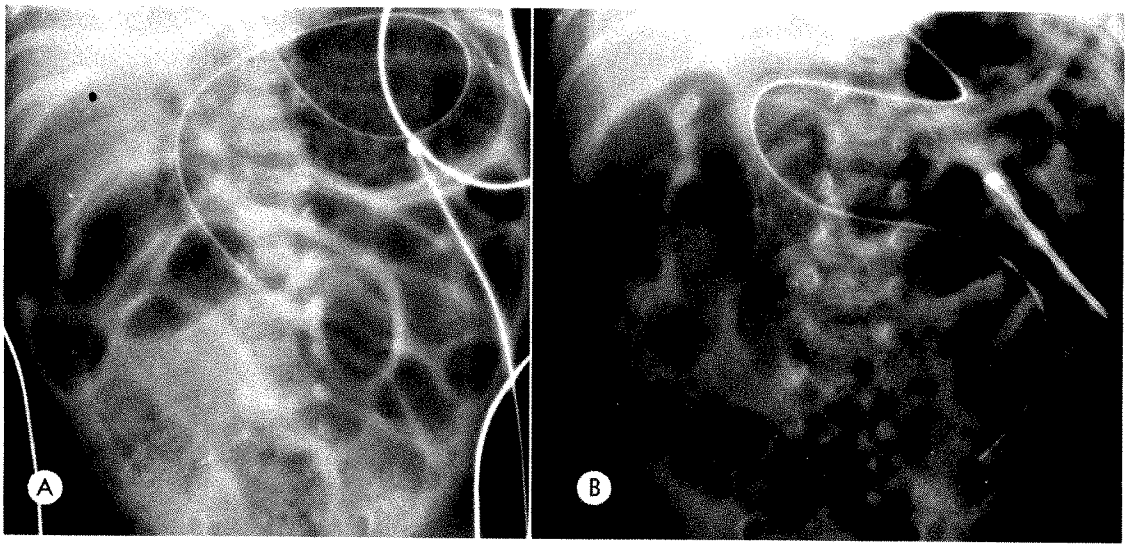

FIG. 7. (*A*) A 950 gm infant who developed sudden abdominal distention at 13 days of age. On the abdominal roentgenogram there is extensive small bowel dilatation with intramural streaks of air in the right lower quadrant. This was accompanied by four episodes of bloody diarrhea during the next twelve hours. (*B*) Spontaneous bowel decompression occurred twelve hours later. No further problems arose and no further intramural air is seen. During the following week there was intermittent right-sided bowel distention as seen here.

jacent loops of matted bowel. In the absence of free air, perforation should be suspected when roentgenologic features of fluid accumulation become evident. These features consist of increased haziness within the abdomen, loss of bowel contour, separation of the bowel loops, etc. Leonidas[3] in a recent publication emphasized the significance of fluid accumulation following the presentation of intramural air in NEC (Fig. 6). He considered this a sign of severe clinical deterioration. In a few patients with obvious pneumatosis, perforation was diagnosed following the removal of pus within the peritoneal cavity by needle puncture. Subsequent surgery revealed multiple sites of bowel necrosis with perforation.

Varying degrees of severity. In early publications of NEC, the disease was associated with an almost 100 percent mortality. Although an over-all poor prognosis is still anticipated, recent experience has demonstrated a steadily increasing survival rate which in some areas has approached 60 percent.[1] The severity of the disease has undergone considerable change and, in fact, there are probably many cases with minimal symptoms. In this respect, we have noted infants who presented with abdominal distention, bloody diarrhea, and probable pneumatosis on the abdominal roentgenogram. However, within a few hours spontaneous decompression of the abdomen and disappearance of the bowel air occurred (Fig. 7). One infant, however, continued to have multiple episodes of guaiac positive diarrhea during the next twelve hours and another infant who appeared clinically well demonstrated persistent right-sided bowel distention. Richmond and Mikity[5] have recently described seven infants who demonstrated what they categorized as a benign form of NEC. These infants, as ours, demonstrated mild clinical signs and symptoms related to the gastrointestinal tract and roentgenographic findings suggesting NEC. All did well with medical management. We are convinced, as others are, that there are varying gradations of bowel ischemia and that some infants may present with only transient episodes of bowel distention, guaiac positive stools, etc. Without obvious confirmation, the diagnosis of NEC cannot be fully established.

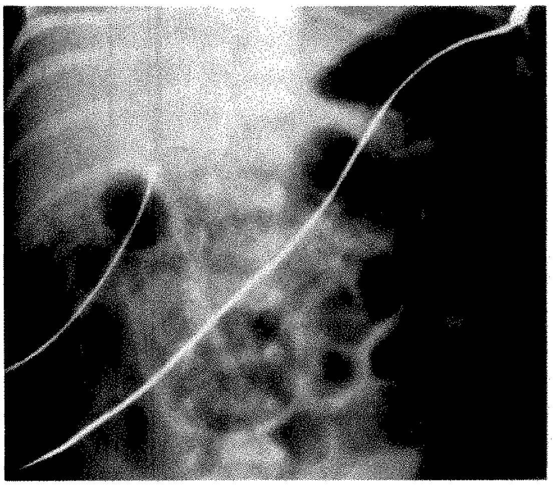

Fig. 8. Three day old premature infant with vomiting and abdominal distention. There are stippled lucencies of cystic pneumatosis in the right side of the abdomen as well as linear pneumatosis.

Pneumatosis intestinalis. The characteristic features and distribution of intramural air have been well described. The pattern varies from a localized mottled or cystic collection of air to diffuse linear collections that frequently outline an extensive area of the wall (Fig. 8). The difference in presentation may depend upon the anatomic location. Gas presenting in a linear appearance is probably located mainly within the muscularis and subserosa, and the cystic presentation is due to gas located within the submucosa. The early roentgenographic manifestations of pneumatosis interestingly enough consist of cystic-bubbly collections of air within the ileocecal region. As the disease progresses and the air dissects deeper into the wall a linear or curvilinear appearance becomes evident.

Although pneumatosis has been considered an absolute criterion for diagnosis of necrotizing enterocolitis, it must be reemphasized that this finding is by no means specific. It has been found in a variety of benign instances, *e.g.*, children with milk intolerance and in patients without evidence of superimposed necrotizing enterocolitis. In the latter case, air enters the bowel wall because of mechanical tear of the mucosa in a distended bowel. The presence of pneumatosis following intra-arterial or intravenous umbilical catheter placement should suggest vascular thrombosis with superimposed bowel necrosis. In general, the presentation of mottled cystic air collections in the right lower quadrant must be distinguished from meconium ileus, the meconium plug syndrome, and inspissated milk syndrome. In most cases, the associated clinical picture is helpful.

DISCUSSION

The cause of NEC is unclear and multiple factors may be responsible for its occurrence. Santulli[6] lists three conditions that must be present for the disease to occur: (1) feeding; (2) mucosal damage; and (3) bacteria. The most important underlying pathogenic process is mucosal damage. In some institutions, the disease has been noted to occur only after the infant has begun to feed. It is possible that feeding of hyperosmolar solutions may be responsible, and infants nutured on maternal milk may demonstrate some degree of resistance to the disease. The antibodies, lymphocytes, macrophages, etc. transported in maternal milk temporarily protect the infant's bowel until he adequately matures to establish his own defenses. Another important factor frequently associated with NEC is stress. Stress, however, occurs under many conditions. In the premature this is most frequently associated with hypoxia. The latter stimulates a physiologic reflex that causes selective shunting of blood away from the bowel to areas of greater need, *e.g.*, heart and brain. The resulting hypoperfusion of bowel results in the loss of many factors that protect the bowel, *e.g.*, mucus, and at the same time causes direct damage to the bowel wall itself. Bacterial proliferation then occurs with invasion of the bowel wall producing intramural air and many other associated changes.

The changing clinical and roentgenographic spectrum presently encountered in NEC is unexplained but in one way or another is related to variations in the severity of the disease. The unsuspecting neonatalogist may also be partially responsible. The aggressive therapy given to premature infants has increased their over-all survival rate and as a result the number of infants now susceptible to the disease has also proportionately increased. In addition, a higher degree of suspicion and better diagnostic criteria in association with an aggressive therapeutic approach to the disease are probably other factors responsible for the changing patterns.

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ARTERIOGRAPHIC MANIFESTATIONS OF PHEOCHROMOCYTOMA*

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ABSTRACT:

Fourteen patients with 16 pheochromocytomas were studied arteriographically over a seven year period. Abnormalities identified the tumor site in 15 instances, but only a single subtle change was present in six of these. Renal artery stenosis was present in eight instances and was significant initially in at least one patient and may become significant in others. A hypertensive response to the study occurred in one-half the patients even though most had received adrenergic blocking drugs. Phentolamine remains the drug of choice in treatment.

THE clinical manifestations of pheochromocytoma are due to excessive catecholamine production. If the tumor produces epinephrine, the symptoms of tachycardia, sweating, apprehension, and hypermetabolism with a tendency toward hyperglycemia and frank diabetes mellitus result. The blood pressure is usually elevated during periods of secretion. Norepinephrine secreting tumors are characterized by systemic vasoconstriction with resultant hypertension. Most tumors produce primarily norepinephrine or a combination of norepinephrine and epinephrine.[13] Catastrophic events such as hypertensive encephalopathy,[51] cerebrovascular accident,[45,47] congestive failure,[4] cardiomyopathy,[13] myocardial infarction,[47] cardiovascular collapse,[24,51] or eclampsia[24] may be the initial presentation of a patient with pheochromocytoma. Classic symptoms include episodic hypertension associated with headaches, nausea, apprehension, diaphoresis, and palpitation. Early symptoms may be more mundane and mimic menopause or essential hypertension (Table I). Unusual symptoms include diabetes insipidus[11] and psychosis.[33] Some patients have no hypertension.[31]

Any symptomatology suggesting pheochromocytoma necessitates the measurement of urinary catecholamines or their metabolites (metanephrine, normetanephrine, and vanillylmandelic acid). In almost all patients with pheochromocytoma, one or more of these substances will be found in excess.[18,21,47] Homovanillic acid excretion, an indicator of biochemical immaturity, has been associated with malignant tumors in adults.[18]

LOCATION AND OCCURRENCE[3,15,16,18,24,25,33,35,39,40,46,48,49]

Pheochromocytomas are located at sites of migration of cells of neural crest origin. All reported primary tumors have been axial, from the base of the skull to the pelvic floor. Most (90 percent) occur in the adrenals and ten percent of these are bilateral. The majority of the remainder of the tumors occur adjacent to the abdominal aorta above or below the renal arteries. Occurrence in the chest or pelvis is next in frequency, and tumors rarely occur in the neck. Multiple tumors are found in about 15 percent of adult patients and 40 percent of children. Up to 80 percent of patients with Sipple's syndrome have bilateral adrenal pheochromocytomas. Multiple tumors usually occur synchronously but may appear over a number of years (asynchronously). There is familial occurrence of pheochromocytoma in approximately ten percent of patients. Familial occurrence is associated with neurofibromatosis, von Hippel-Lindau's disease and Sipple's syndrome. Approximately ten percent of pheo-

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TABLE I

CLINICAL MANIFESTATIONS

Patient	Age—Sex	Presenting Complaint	Location
P.T.	9 M	Recent onset of acute glomerulonephritis and hypertensive encephalopathy	Bilateral adrenal
B.G.	27 F	Headaches for 4 years; worsening headaches and hypertension 1 year	Left renal pedicle
P.G.	31 F	Episodic headaches with nausea and vomiting for 3 years; documented hypertension for 1 month	Right adrenal
A.N.	32 M	Excessive diaphoresis for entire life; hypertension for 18 years	Right adrenal
M.D.	47 F	Episodic nausea, tachycardia, pilo-erection, headache, and diaphoresis for 5 years; abnormal glucose tolerance test for 5 months; poorly documented elevation of blood pressure	Left adrenal
F.B.	48 F	Family history Sipple's syndrome; multinodular goiter	Right adrenal*
A.P.	49 F	Episodic mild headaches and "hot flashes" with irregular menses for 3 years; increasing severity headaches and "hot flashes" with associated nervousness, diaphoresis, and flushing for 3 months; documented hypertension for 6 weeks	Para-aortic undersurface of diaphragm
S.W.	50 M	Mild hypertension for 1 year; severe left chest pain with dyspnea and diaphoresis for 1 day	Left adrenal
G.G.	52 F	Evaluation of recurrent thyroid cancer; diarrhea for 4 years	Bilateral adrenal
L.S.	53 F	Hypertension for 6 years; episodic headaches, flushing, tachycardia, diaphoresis, and chest pain (sometimes associated with micturition) for 2 months	Urinary bladder
J.M.	54 M	Numbness and weakness of left upper and lower extremities for 6 weeks	Right adrenal
S.M.	58 F	Episodic shortness of breath, palpitation, sweating, nausea, vomiting, and tremulousness for 3 years; diabetes mellitus and hypertension for 18 months	Para-aortic near celiac axis
T.S.	60 F	Episodic weakness, tremor, flushing, diaphoresis, tachycardia, headache, nausea, and vomiting complicating the postoperative recovery period from pelvic surgery 6 months prior to admission	Right adrenal
C.D.	65	Hypertension for 15 years; syncopal attack 3 weeks prior to admission	Right renal pedicle

* Left adrenal was also removed; it showed some pleomorphism but no gross tumor; it was not included as a pheochromocytoma in this study.

chromocytomas are malignant by virtue of distant metastasis.

METHODS OF TUMOR LOCALIZATION

Tumors in the cervical region are usually found on physical examination.[16,41] Thoracic tumors are almost always demonstrated by chest roentgenography and are usually paravertebral in location, although mediastinal occurrence has also been reported.[13]

Abdominal roentgenograms and intravenous urography often reveal the location of tumors by virtue of calcification[20] or mass effect on the urinary tract,[27] or both (Fig. 1).

Retroperitoneal gas insufflation is primarily of historical interest because of fre-

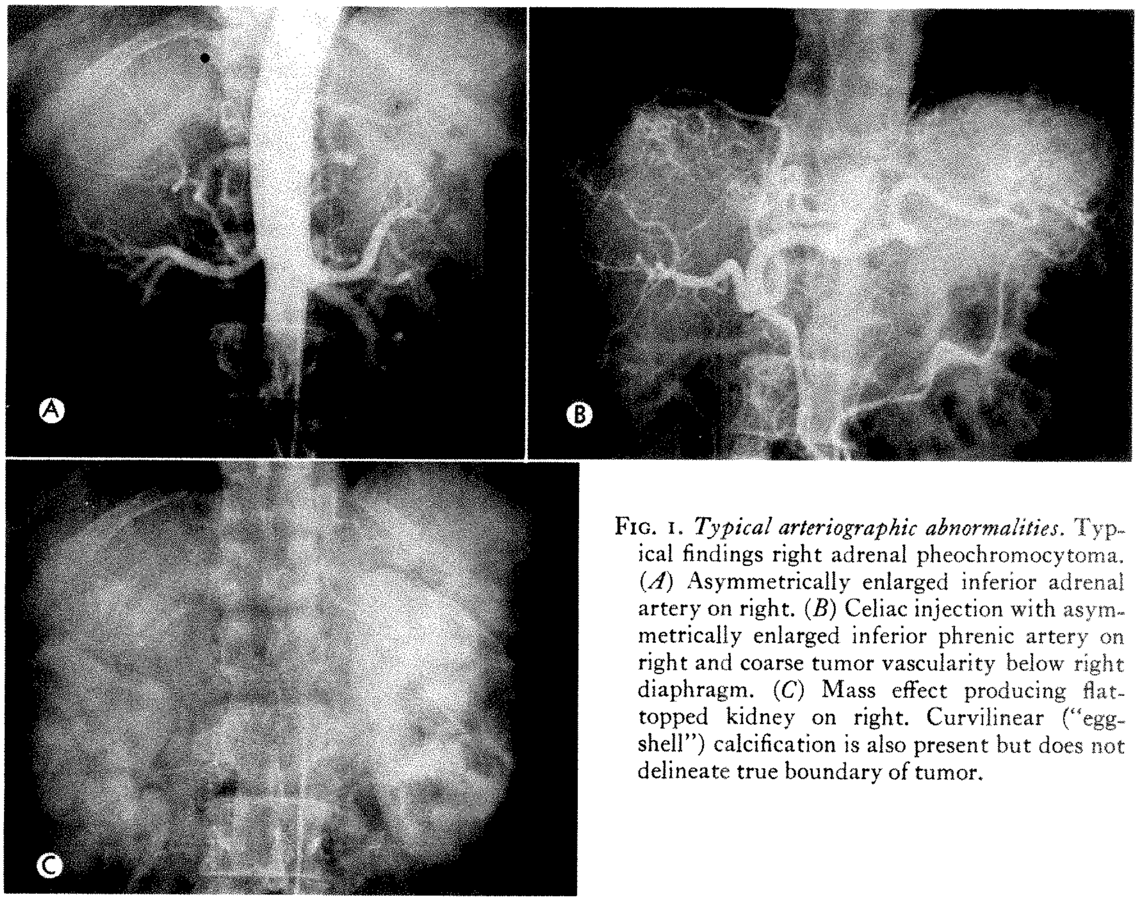

FIG. 1. *Typical arteriographic abnormalities.* Typical findings right adrenal pheochromocytoma. (*A*) Asymmetrically enlarged inferior adrenal artery on right. (*B*) Celiac injection with asymmetrically enlarged inferior phrenic artery on right and coarse tumor vascularity below right diaphragm. (*C*) Mass effect producing flat-topped kidney on right. Curvilinear ("egg-shell") calcification is also present but does not delineate true boundary of tumor.

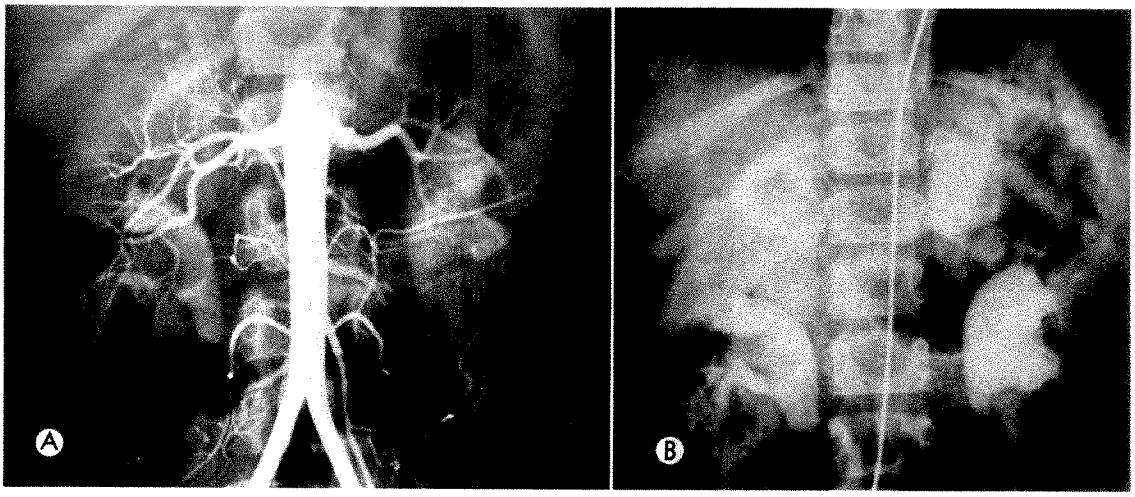

FIG. 2. *Typical and single abnormality in same patient.* Patient with bilateral adrenal pheochromocytomas of the same size. (*A*) Asymmetrically enlarged inferior adrenal arteries. (*B*) Blush over both upper poles. Gaseous distention of the stomach would have been of advantage to show this on the left.

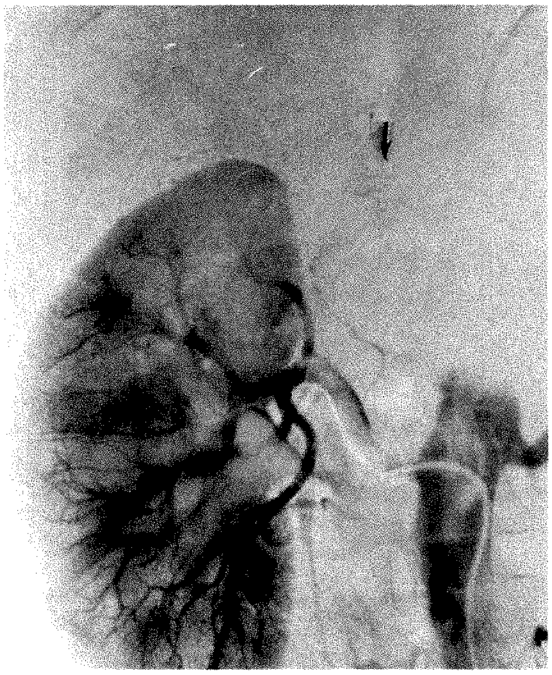

FIG. 3. *Subtle arteriographic abnormality.* Subtraction film in patient with retrocaval pheochromocytoma. A small collection of tumor vessels is present in prevertebral area. Inferior adrenal artery is normal in size.

quent difficulties in interpretation and significant morbidity associated with the procedure. Adrenal venography can more accurately diagnose adrenal tumors,[8,19,37] but cannot exclude synchronous tumors of extra-adrenal origin.

Vena cava sampling for catecholamines has been successful in tumor localization.[34] However, the method of serum catecholamine assay is not generally available.[18]

Arteriography is advantageous for preoperative localization of pheochromocytomas. No mortality nor significant morbidity has been related to arteriography during the past 16 years.[1,5–7,9,11,12,14,17,28–30,32,35,36,38,42,43,51,52] Most pheochromocytomas are vascular and demonstrate large feeding vessels and tumor blush (Fig. 2), but infarction, necrosis, and cyst formation may preclude demonstration of tumor vascularity.[5]

In vascular tumors,[29] enlarged feeding vessels may encircle the mass. A spoke-like arrangement of smaller arteries may enter the tumor or a fine reticular pattern of vessels may be present within the tumor. A capillary blush is often present and may be dense and homogeneous throughout the tumor. In the presence of infarction or necrosis the blush may be less dense and occupy only portions of the tumor mass. Capsular veins may be demonstrated de-

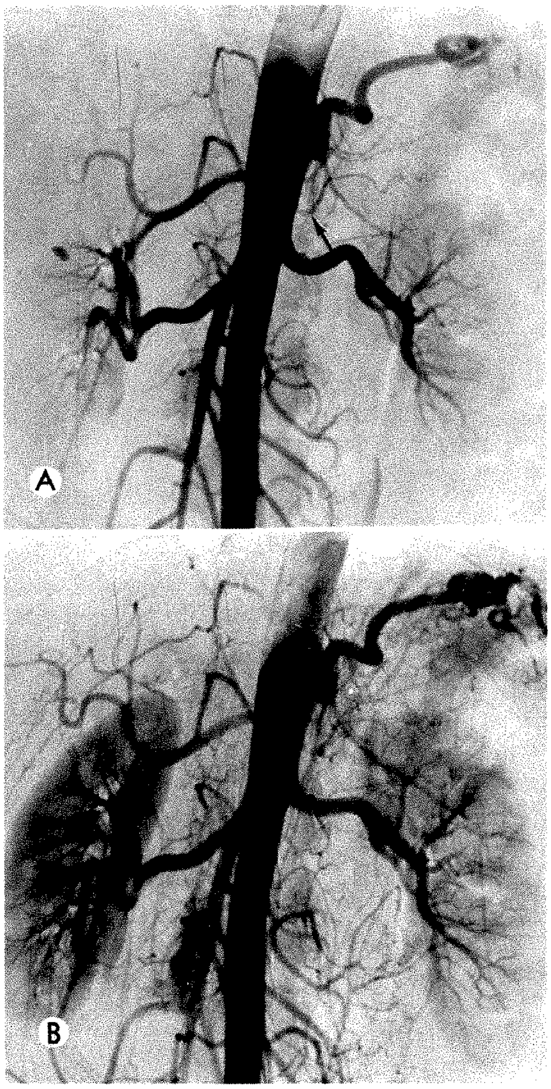

FIG. 4. *Subtle arteriographic abnormality and false positive.* Subtraction film showing (*A*) enlarged vessel—probably middle adrenal—with stenotic origin arising from aorta in patient with left adrenal pheochromocytoma. (*B*) Hypervascular area right lumbar paravertebral area. No abnormality was found here at surgery.

pending on the amount of contrast material used and the length of filming, but should not be considered necessary for the diagnosis.

Renal artery stenosis has been associated with pheochromocytoma. The lesions may be attributed to tumor encasement, local arterial reaction to elevated tissue levels of catecholamine, arteriosclerotic plaques, fibromuscular hyperplasia, or fibrosis associated with neurofibromatosis.[2,38]

MATERIAL AND METHOD

Arteriography has been employed in 14 patients with 16 tumors from 1967 to 1974. There were nine females and five males ranging in age from nine to 65 years. Eleven tumors were adrenal and five extra-adrenal (two para-aortic, two renal hilum, and one bladder). In three patients the diagnosis had not been made prior to arteriography. The eleven remaining patients had adrenergic blockade prior to the study.[10,18,21,44,47]

A thorough review of plain films and intravenous urograms preceded each arteriographic examination. Abdominal aortography was performed initially and was usually followed by selective renal injections. In more recent years pelvic arteriography has been routinely performed as well. Selective lumbar, middle adrenal, celiac, and superior mesenteric injections were performed in specific instances to evaluate further the presence of tumor or to demonstrate its blood supply.

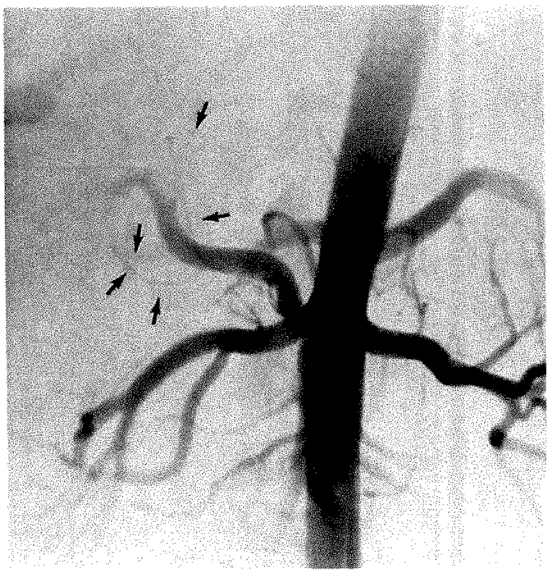

Fig. 5. *Single arteriographic abnormality.* Subtraction film showing several encircling vessels in right adrenal area at site of an adrenal pheochromocytoma. No blush occurred during capillary phase. Stenosis at the origin of the ventral branch of the right renal artery is also present.

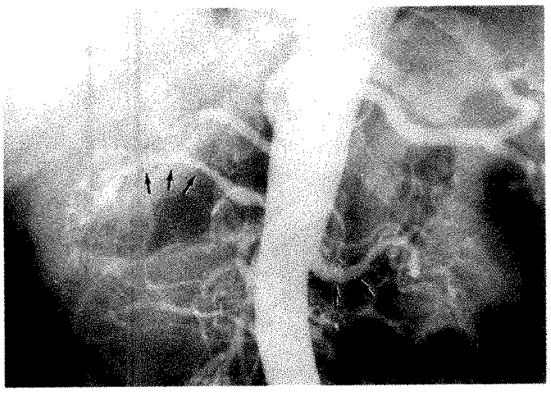

Fig. 6. *Renal artery stenosis.* Large pheochromocytoma below right renal artery causing upward displacement and narrowing of the right renal artery. There is contour irregularity of left renal artery as well.

In all patients in whom the diagnosis of pheochromocytoma was suspected, an intravenous infusion was maintained during the arteriographic examination. Phentolamine and an emergency cart are always at hand. Attendance of the clinician is recommended to help monitor the patient and provide assistance in the management of any emergencies.

RESULTS

Prospective evaluation of the arteriograms localized eleven of 16 tumors. Tumor was suggested four times where none existed[14,30] (Fig. 4; and 7). The five tumors not recognized were located within the adrenal gland (Fig. 8). Retrospective analysis of these studies showed abnormalities present in four examinations. The one tumor for which there were no arteriographic findings was 2 cm in diameter and occurred in a patient with Sipple's syn-

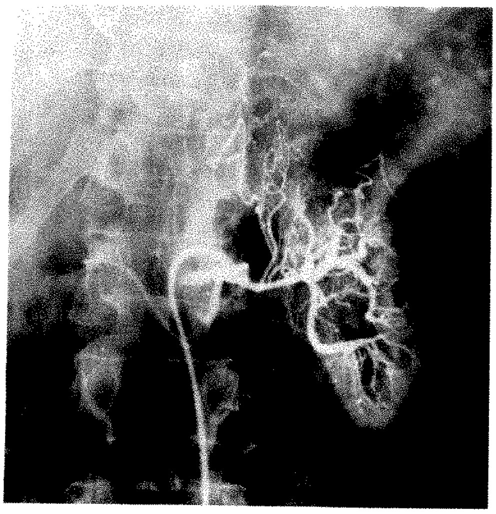

Fig. 7. *False positive arteriogram.* Study in patient with right adrenal pheochromocytoma. Selective injection on opposite side shows atrophic kidney and enlarged tortuous adrenal vasculature with poor definition of superior pole of kidney. Left adrenal gland normal at surgery.

drome. Table II lists the findings in the remainder of the patients.

A hypertensive response occurred during seven of the 15 arteriographic studies (one patient was studied twice). This occurred in two of three patients without and five of eleven patients with prior adrenergic blockade. This usually, but not always, occurred with injection of the feeding vessel. In one patient, the hypertensive response occurred after the completion of the procedure and lasted for two hours. The hypertensive responses secondary to arteriography did not result in additional morbidity, but in most instances required treatment to control blood pressure.

In three patients there was stenosis at the origin of an enlarged feeding vessel. In one patient this was the only visible abnormality, and pathologic examination revealed an infarcted tumor. This finding has not been previously reported. Its significance and etiology are unknown.

DISCUSSION

Arteriographic findings in pheochromocytoma may be obvious or subtle (Fig. 3), but almost always are present. Gaseous distention of the stomach is recommended so that tumor blush is not mistaken for gastric capillary blush, and so that the arteriographic pattern in the left adrenal gland may be optimally visualized. Inferior phrenic and inferior adrenal arteries must be well visualized and evaluated for asymmetry.[26] Subtraction is an important adjunct procedure for the demonstration of sparse tumor vascularity[42] (Fig. 5).

Although renal artery stenosis has been reported as a rare finding associated with pheochromocytoma,[6,38,50] some degree of stenosis (Fig. 6) was present in eight of 27 renal arteries in this study (the 28th was atrophied presumably secondary to pyelonephritis). In one patient, renal artery stenosis contributed to hypertension as evidenced by renal vein renin assay.[50] Although not apparently significant in other patients at the time of initial arteriography, recurrent hypertension in treated patients would necessitate evaluation not only for recurrent tumor but for the development of significant renal artery stenosis as well.

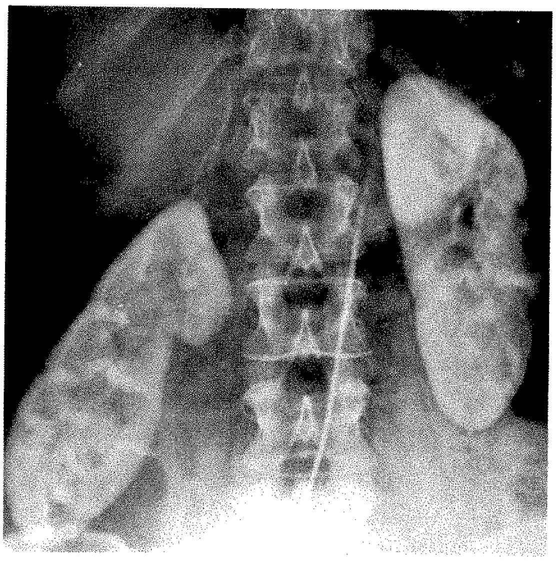

Fig. 8. *False negative arteriogram.* Patient with 2 cm right adrenal pheochromocytoma. Capillary phase of arteriogram reveals normal appearing blush of right adrenal gland. No abnormal vessels were present during arterial phase.

Hypertensive response to contrast material injection may occur in those patients thought to be protected by adrenergic blockade. Phentolamine should be administered slowly in a 2.5 to 5 mg intravenous bolus to titrate the blood pressure. A more dilute solution such as 5 mg in 500 cc of five percent dextrose in water should be infused at a rate sufficient to maintain the effect. Tachyarrhythmias of nodal or conduction system origin may occur due to excessive beta adrenergic stimulation, especially in the presence of hypertension. Blood pressure elevation should be controlled first, and if arrhythmia persists, lidocaine should be administered slowly in a bolus of 50 to 100 mg intravenously. Volume expanders and pressor agents should be employed in the event that hypotension occurs.[18,21,47]

SUMMARY

Fourteen patients with 16 pheochromocytomas have been studied by arteriography. Evidence of tumor was present in all but one instance (a 2 cm adrenal tumor). In three instances there was stenosis of the feeding artery. In six instances only a single finding was present (central vascular network, encircling collection of vessels, deviated vessels, blush, or enlarged feeding artery). Significant renal artery stenosis was present in one patient. In three patients pheochromocytoma was unsuspected prior to arteriography. Hypertensive response occurred in five of eleven patients premedicated with adrenergic blocking agents. Careful monitoring of the patient during and after examination is necessary to recognize complications as the result of arteriography.

Table II

ARTERIOGRAPHIC ABNORMALITIES

- Multiple Criteria—9 tumors
  - enlarged feeding artery
  - tumor vascular network
  - capillary blush, mass effect, or both
- Single Criterion Only—6 tumors
  - encircling collection vessels
  - deviated vessels
  - small collection tumor vessels
  - blush obscured by stomach
  - enlarged feeding vessel with stenotic origin
  - flash filled asymmetrically enlarged inferior phrenic artery
- No Findings—1 tumor
- False Positives—4 instances
  - prominent adrenal vascular network on side of atrophic kidney
  - large inferior adrenal artery with prominent adrenal vascular network
  - dense blush over right inferior margin third lumbar vertebral body
  - small collection vessels left border first lumbar vertebral body

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EMBOLIC OCCLUSION OF THE SUPERIOR AND INFERIOR DIVISIONS OF THE MIDDLE CEREBRAL ARTERY WITH ANGIOGRAPHIC-CLINICAL CORRELATION*

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ABSTRACT:

Clinicians, in defining cerebral vascular syndromes, recognize embolism to the superior and inferior divisions of the middle cerebral artery in addition to embolism of the individual branches. In the present study 14 examples of arteriographically visualized divisional occlusion are analyzed, and a good correlation is demonstrated between the roentgenologic and clinical findings.

THE branching pattern of the middle cerebral artery (MCA) is variable and a variety of MCA nomenclatures has been suggested.[1,5,6,8–10] As early as 1958, in the clinico-pathologic interpretation of embolic strokes in the MCA territory, neurologists have recognized two main divisions of the MCA, a superior and an inferior. The cor-

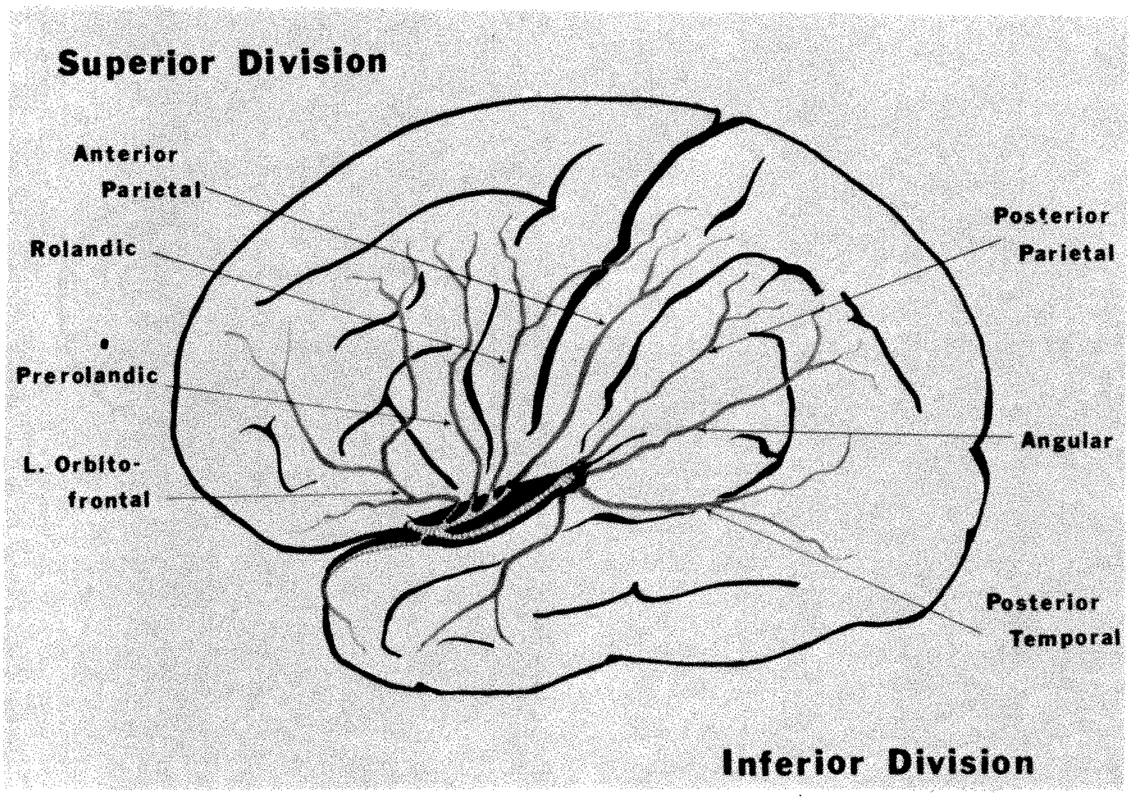

FIG. 1. Diagram illustrating the classical branching pattern of the superior and inferior divisions. Central sulcus between anterior parietal and rolandic arteries separates areas of motor from sensory functions.

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Table I

ANGIOGRAPHIC LOCALIZATION OF MIDDLE CEREBRAL OCCLUSIONS

Location	No. of Cases	Approximate Percent
Proximal stem*	5	6
Distal stem	27	32
Superior Division	9	10
Inferior Division	5	6
Combined division (saddle)	13	15
Distal branches	25	30
Total	84	

* Prior to origin of striate arteries.

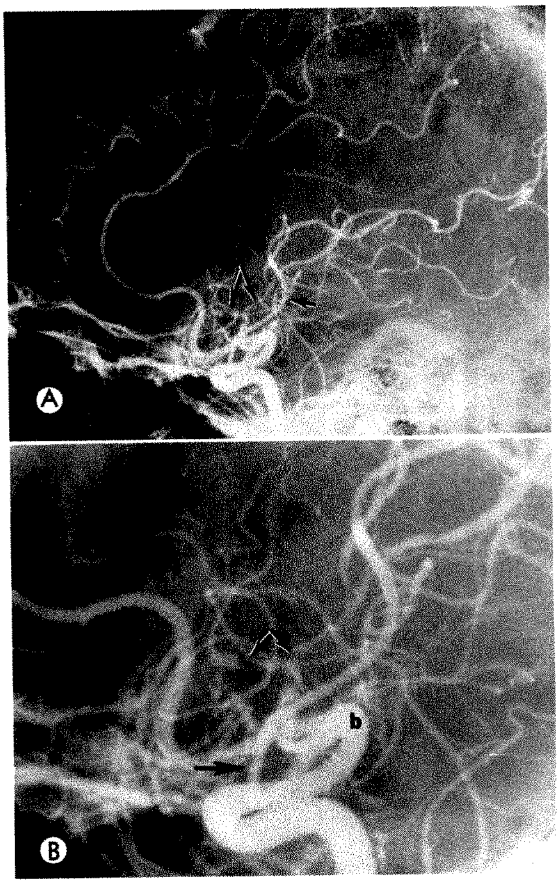

Fig. 2. (*A*) Superior division embolus (arrows) extending into proximal branches. Large frontal avascular zone results from occlusion. Inferior division including its branches appears normal (arrow). (*B*) Photographic enlargement of superior division embolus (arrows), bifurcation of both divisions (b) and normal appearing inferior division (large arrow).

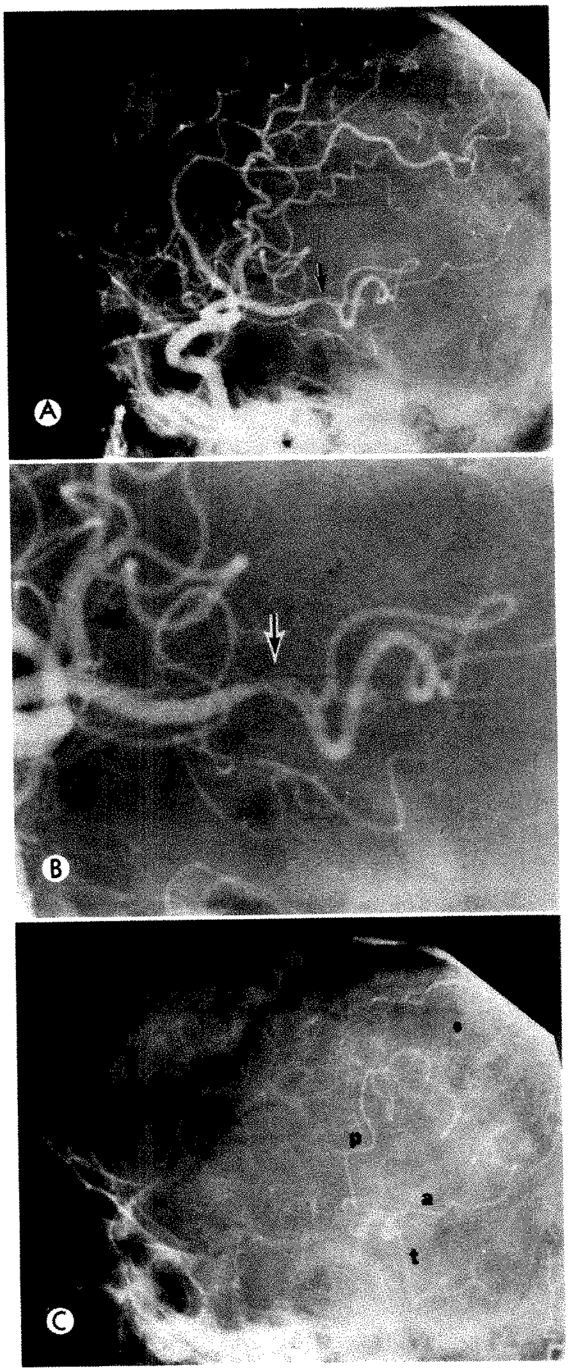

Fig. 3. (*A*) Embolus within distal inferior division (arrow). Superior division identified by arrowhead. (*B*) Photographic enlargement of normal superior division (arrowhead) with embolus in inferior division (arrow). (*C*) Late arterial phase demonstrating slow antegrade flow within the three major branches of the inferior division: posterior parietal (p), angular (a), and temporal (t).

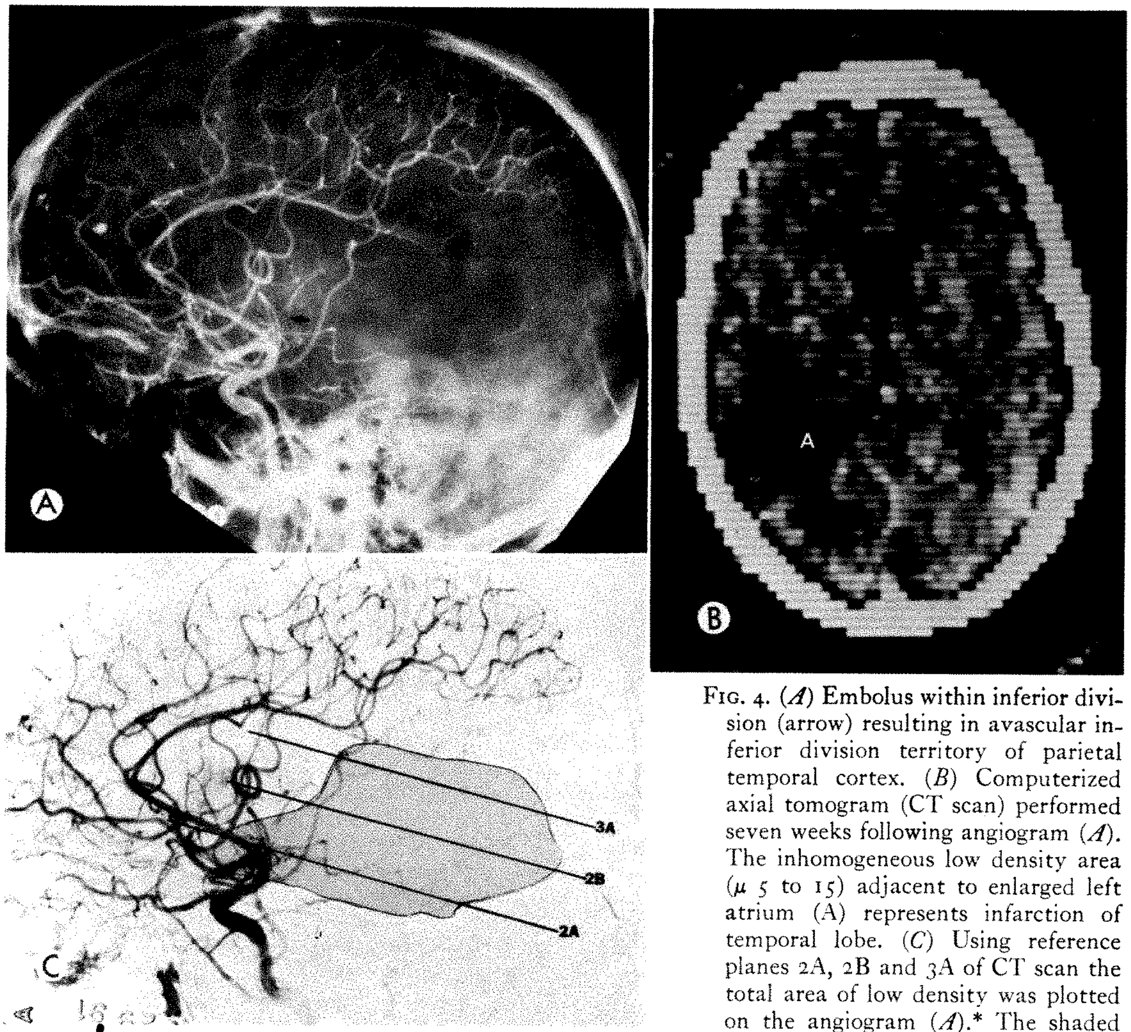

FIG. 4. (*A*) Embolus within inferior division (arrow) resulting in avascular inferior division territory of parietal temporal cortex. (*B*) Computerized axial tomogram (CT scan) performed seven weeks following angiogram (*A*). The inhomogeneous low density area (μ 5 to 15) adjacent to enlarged left atrium (A) represents infarction of temporal lobe. (*C*) Using reference planes 2A, 2B and 3A of CT scan the total area of low density was plotted on the angiogram (*A*).* The shaded area indicates extent of infarction and corresponds to territory supplied by the inferior division.

* The three reference levels at 2.5 cm intervals are superimposed on angiogram using inner table of skull and Reid's baseline as common reference points. Measurements were corrected for magnification difference.

responding angiographic definition of divisional MCA occlusion is undertaken in the present study.

We define a classic superior division as a major trunk consisting of four ascending branches, the lateral orbitofrontal, prerolandic, rolandic, and anterior parietal; while the inferior division consists of the remainder of the MCA branches, namely, posterior parietal, angular, and temporal arteries (Fig. 1). Minor exceptions to this model are commonly definable angiographically; *e.g.*, the orbitofrontal branch may arise from the distal main MCA stem* rather than the proximal superior division, or the anterior temporal may originate from the distal MCA system rather than the proximal inferior division. Thus is explained the escape of one or both of these branches in distal MCA occlusion by a large embolus arrested at the point where the MCA bifurcates into its two divisions. Posteriorly, the anterior parietal branch may arise from the inferior division rather than the superior. Despite these anatomical variations, a superior division supplying three or four individual branches is present in 90 percent of anatomic specimens.

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* The term stem refers to the section of superficial artery lying between the origin of the MCA and the first major branch.[4]

MATERIAL

Eighty-four angiographic examples of occlusion of the MCA or its branches were reviewed (Table I) and from this group 14 satisfying our angiographic criteria of division occlusion were selected for special study. In addition the clinical manifestations of the eleven cases with divisional occlusion in the left or dominant hemisphere were analyzed.

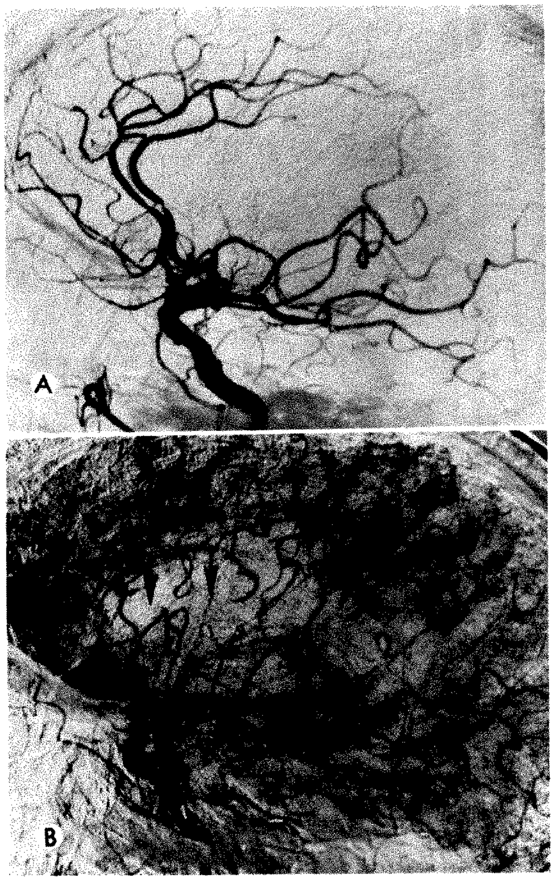

FIG. 5. Total occlusion of superior division. (*A*) Large frontal avascular zone resulting from superior division occlusion. (*B*) Later arterial phase of (*A*) showing simultaneous retrograde filling of superior division branches (arrows).

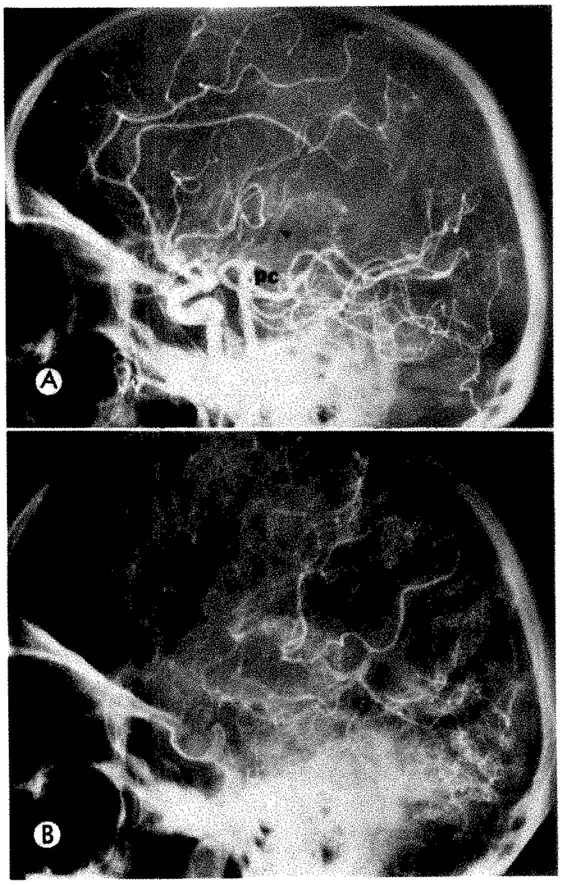

FIG. 6. (*A*) Retrograde right brachial arteriogram showing avascular parietal-temporal zone resulting from total occlusion of inferior division. Flash filling of opposite hemispheric MCA branch indicated by arrowhead. (*B*) Reconstitution of the three major branches of the inferior division$^{1-3}$ by retrograde collateral circulation primarily from the post cerebral artery (PC).

RESULTS

Division occlusion by an embolus was angiographically defined either by demonstrating a filling defect within the lumen (Fig. 2–4) or by demonstrating abrupt total occlusion of the division with simultaneous retrograde filling of all its major branches by collaterals (Fig. 5; and 6). Intraluminal filling defects representing emboli were visible in four of 14 cases while the remainder showed total occlusion with reconstitution by retrograde flow. Collateral filling of superior division branches was

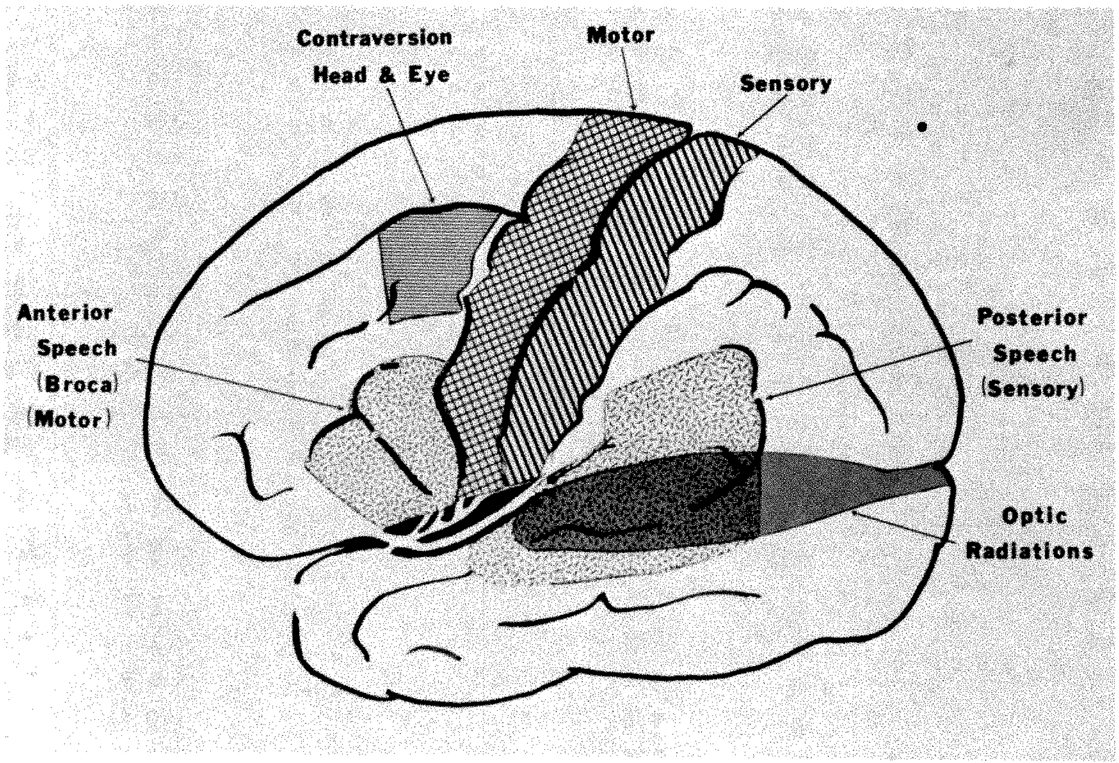

Fig. 7. Functional areas of dominant hemisphere. Motor and sensory areas separated by central sulcus and in turn perfusion territories of superior and inferior divisions. Compare with Figure 1.

furnished by multiple branches of the ipsilateral anterior cerebral artery, while inferior division branches were reconstituted by multiple branches of the ipsilateral posterior cerebral artery or the pericallosal artery, or both. Callosomarginal arteries in the cingulate sulcus never participated in collateral flow to inferior division territory.

Clinical-angiographic correlations were undertaken in the eleven cases involving occlusion in the dominant hemisphere with aphasia. Clinicians have found that embolism to the superior division causes a hemiplegia and motor aphasia due to infarction of the motor cortex and Broca's area respectively, whereas embolism to the inferior division does not cause a hemiplegia nor paralysis since the motor area of the brain is spared, but gives rise to Wernicke's aphasia as a result of infarction of the temporal lobe[2,3] (Fig. 7). It was to examine this clinico-pathologic rule that the eleven cases were analyzed.

Six of seven patients with superior division occlusion showed severe hemiplegia with motor aphasia while all four patients with inferior division occlusion exhibited sensory receptive aphasia without motor weakness. Three of four inferior division occlusions had a hemianopia. This excellent correlation of the clinical and roentgenological findings during the acute phase of the illness strongly supported the conclusions derived from pathologic studies.

In the past, clinical manifestations have been correlated with angiographically proved occlusion of individual branches of the MCA.[7,11] The concept of division occlusion, however, has not been clearly formulated. We have found it very useful in increasing the precision of clinico-angiographic correlation. Moreover, appreciation of the anatomy of divisions assists in understanding the angiographic distribution of embolic fragments and in interpreting the clinical picture in what appear to be partial or incomplete divisional syndromes. Magnification and subtraction techniques should be employed for optimal visualization of intraluminal emboli and consideration should be given to visualizing the various routes of collateral circulation, particularly if none is visible by unilateral carotid injection. This is particularly true of inferior division occlusion where collateral vessels may be demonstrated only by opacification of the posterior cerebral artery (Fig. 6). Since the cervical carotid may serve as a source of emboli, it should be carefully studied.

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CEREBRAL BLOOD VOLUME ALTERATIONS DURING FRACTIONAL PNEUMOENCEPHALOGRAPHY*

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ABSTRACT:

Simultaneous and continuous measurements of the cerebral blood volume (CBV), cerebrospinal fluid (CSF) and blood pressure were carried out in six patients during fractional pneumoencephalography in order to examine intracranial volumetric interactions. Three patients (Group A) showed normal encephalographic findings, and in three patients (Group B) communicating hydrocephalus with convexity block was found encephalographically. In all patients the injection of air was followed by an immediate increase of CSF pressure and blood pressure and a concomitant decrease of CBV. The initial CSF pressure was invariably re-established within 3 to 3.5 min. During this time interval the CBV of the patients of Group B decreased significantly and 30 percent more than that of Group A. Furthermore, after restoration of the original CSF pressure, CBV returned to its initial level in all patients of Group A, whereas it remained unchanged or showed a further decrease in the patients of Group B. Removal of an amount of CSF corresponding to half of the amount of injected air was followed by a significant reactive hyperemic response in two normal patients. The intracranial volumetric alterations during fractional pneumoencephalography are discussed in detail with respect to the underlying physiologic mechanisms and are suggested as a model for acute and low pressure hydrocephalus.

ALTHOUGH pneumoencephalography has been used extensively in clinical practice for more than 50 years, the basic mechanisms and pathophysiologic events resulting from the insufflation of air into the cranial cavities are far from being clarified. Recently, evidence has shown that the progressive dilatation of the ventricular system, known to take place in conjunction with pneumoencephalography,[18,21,31] occurs early, during the first minutes after the insufflation of air.[22] This dilatation involves the fourth,[28] third,[16] and lateral ventricles[29] and gives rise to the hypothesis that a distending pressure acting on a compliant brain plays a key role among factors influencing ventricular filling.

Cerebrospinal fluid (CSF) pressure recordings during pneumoencephalography have shown the injection of air to provoke an immediate increase in pressure which returns to the original level within a few minutes.[1,11] The pressure increase is usually accompanied by an arterial hypertensive response and bradycardia following the insufflation of air,[35] which are well-known effects of raised intracranial pressure (ICP).[4] The initial compensation of the pressure increase occurs with distention of the dural sac mainly at the spinal level[26] and this is limited.[23] Further compensation can be obtained only by displacement of a corresponding volume of easily movable intracranial contents. Theoretically, this can be accomplished by a decrease of intracranial intravascular fluid, *i.e.*, diminished cerebral blood volume (CBV), or by an increased absorption rate of CSF. The present study with simultaneous pneumoencephalographic and CBV examinations was designed to investigate these volumetric intracranial interactions in an attempt to confirm the theory that the ventricular system is enlarged at the expense of CBV during fractional pneumoencephalography.

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MATERIAL AND METHOD

Patient material: Simultaneous and continuous measurements of the CBV were done in six patients without obvious signs of a focal neurologic lesion during routine encephalographic examinations. The patients ranged in age from 35 to 64, with a mean of 54 years.

Pneumoencephalographic technique: The patients sat in the encephalographic chair in an upright position with the head bent slightly forward against a head support. All examinations were performed without general anesthesia as this may change the intracranial pressure.[6] One lumbar needle was introduced between L4 and L5 for the air injection. A standardized injection technique was usually employed, in regard to both the amount of air injected and the time interval between the injections. Ten milliliters of air were injected two times with a 30 sec interval.

Pressure measurements: The intrathecal pressure was continuously recorded by electromanometric methods, by means of a second needle introduced into the subarachnoid compartment between L3 and L4 as described by Grepe in 1972.[11] Blood pressure was recorded conventionally with a cuff manometer during the whole examination at one to two minute intervals.

Cerebral blood volume (CBV) measurements: After intravenous injection of the radionuclide, continuous measurements of the CBV were made with the detection equipment described below. CBV measurements began after a uniform distribution of the isotope in the blood had been attained, usually three minutes after the injection of the radionuclide. The radioisotope used was ^{113}In^{m} because of the low radiation dose due to its short physical half-life (about 100 minutes) and its lack of β radiation. The contribution to the absorbed dose is mainly due to γ radiation (393 keV) and to internal conversion electrons. For this investigation, acid ^{113}In^{m} ions were eluted from a ^{113}Sn$-^{113}$In^{m} generator, and 2 to 2.5 mCi were injected intravenously. The ^{113}In^{m} ions will immediately be bound to the plasma transferrins, which will not pass the blood brain barrier, thus forming the theoretical basis for their use in blood volume examinations. The activity administered can be estimated to give a whole body dose of about 0.03 to 0.05 rad and a dose to the critical organ (blood) of about 0.3 to 0.5 rad.

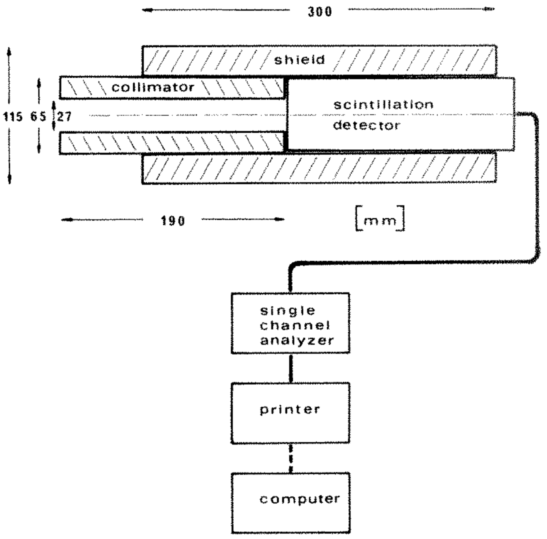

Fig. 1. Diagram of the detection equipment used for CBV determinations and technical data of the collimator.

A sharply collimated NaI detector was used for the detection of the 393 keV γ-radiation. The technical data of the detector are shown in Figure 1. A long collimator was used in order to increase the depth-sensitivity of the detecting system. The detector was placed adjacent to the parietal region of the patients' cranial vaults, thus measuring in an area above the trigone of the lateral ventricle. The position of the detector was controlled with skull roentgenograms before and after the measurements. The signals from the detector were fed into a single-channel analyzer (ELSCINT) with the pulse-height discrimination window set to accept pulses corresponding to the total absorption peak. The measuring performance was made in a

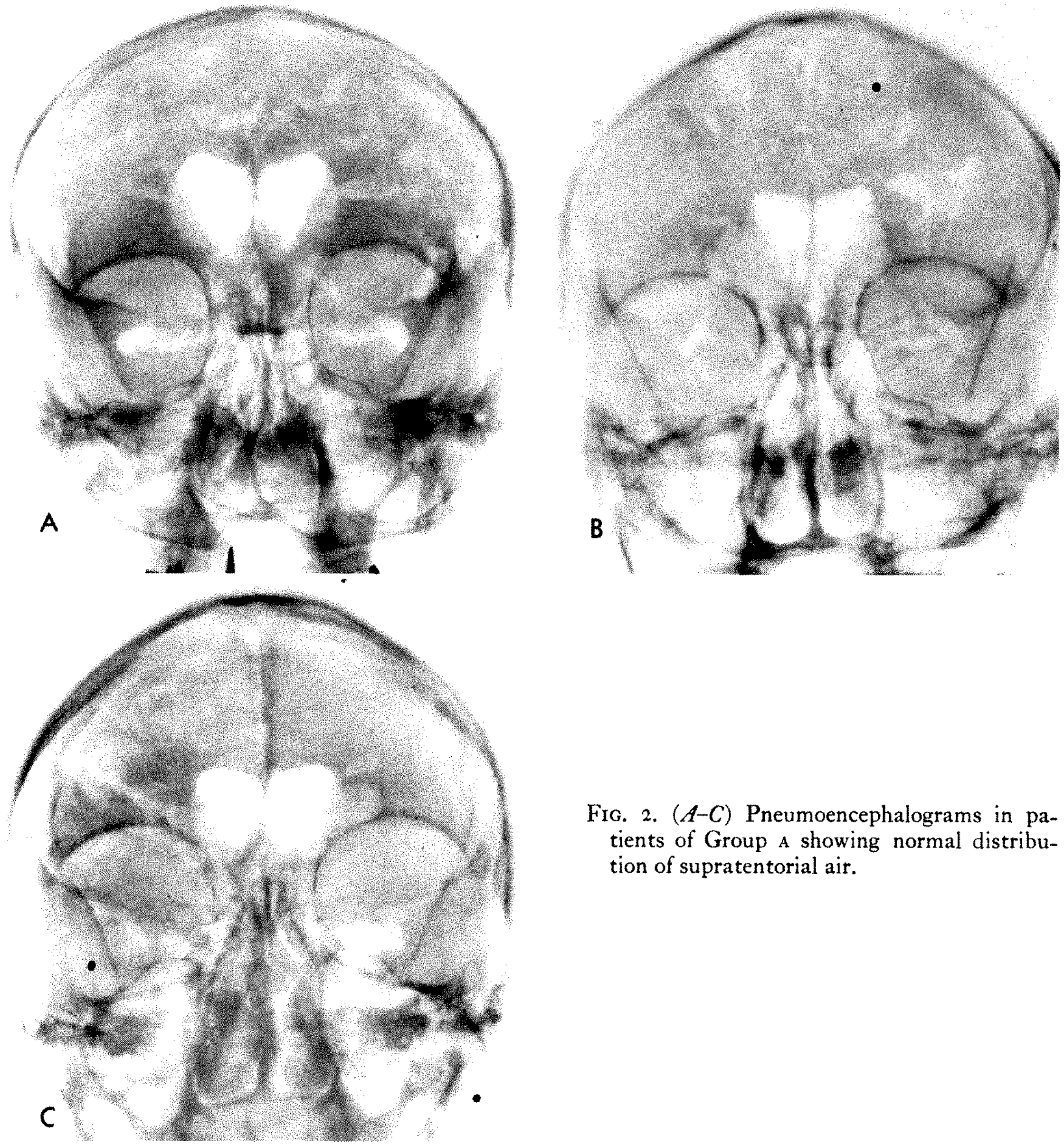

FIG. 2. (*A–C*) Pneumoencephalograms in patients of Group A showing normal distribution of supratentorial air.

recycling mode with measuring time set to 30 sec and a waiting and reset time of about 5 sec. All measured values were printed out automatically after each measuring sequence and the results, corrected for the radioactive decay, were calculated by a ND 812 computer.

RESULTS

In three patients (Group A), ranging in age from 35 to 62 years, with a mean of 47 years, the encephalographic findings were normal with respect to the ventricular size including the width of the temporal horns and to the subarachnoid spaces (Fig. 2). The pneumoencephalographic studies of the other three patients (Group B), ranging in age from 61 to 64 years, with a mean of 62 years, showed convexity block and different degrees of dilatation of parts or the total ventricular system indicating various stages of communicating hydrocephalus (Fig. 3).

A typical CBV curve with corresponding

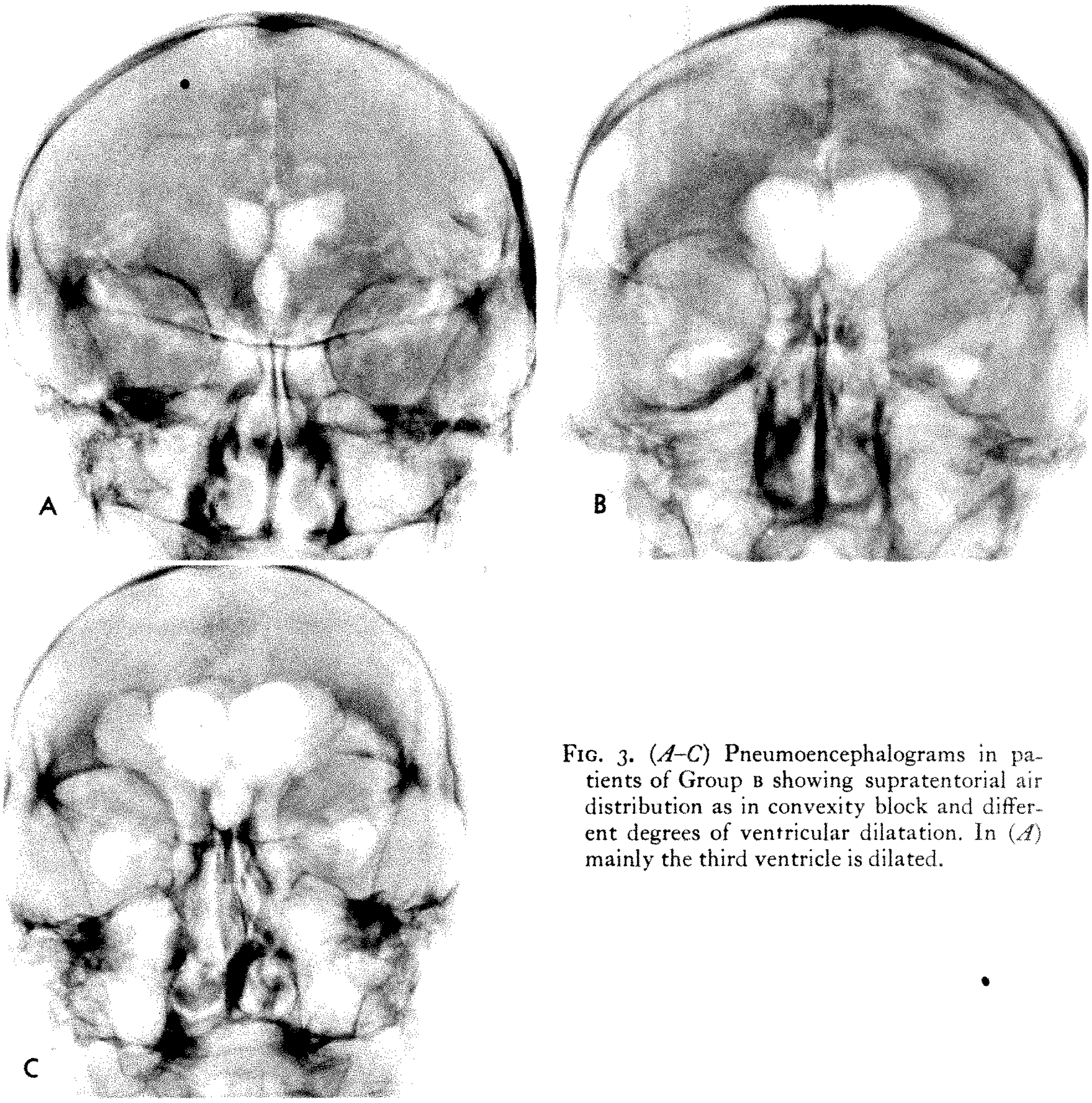

FIG. 3. (*A–C*) Pneumoencephalograms in patients of Group B showing supratentorial air distribution as in convexity block and different degrees of ventricular dilatation. In (*A*) mainly the third ventricle is dilated.

CSF and blood pressure curves in a normal subject appears in Figure 4. The significantly different CBV curve in a patient with convexity block is shown in Figure 5. Figure 6 shows the schematic drawing of the mean CBV curve derived from the three normal patients in comparison to the CBV curve from those with convexity block. The mean of the initial 10 CBV measurements was set to 100 percent in all patients (Fig. 4; 5; and 6, part I). The successive injections of 10 ccm of air were made twice and were immediately followed by a decrease of CBV and a concomitant increase of CSF pressure and blood pressure in all patients (Fig. 4; and 5, part II). The mean CBV remained decreased until the CSF pressure returned to its original level (Fig. 4; and 5; part III). The patients with convexity block showed a reduction of CBV which was at an average 30 percent greater than that of normal patients (Fig. 6, part III). After restoration of the initial CSF pressure during a time interval of 3 to 3.5 min a mean increase of CBV almost to 100 percent of the original

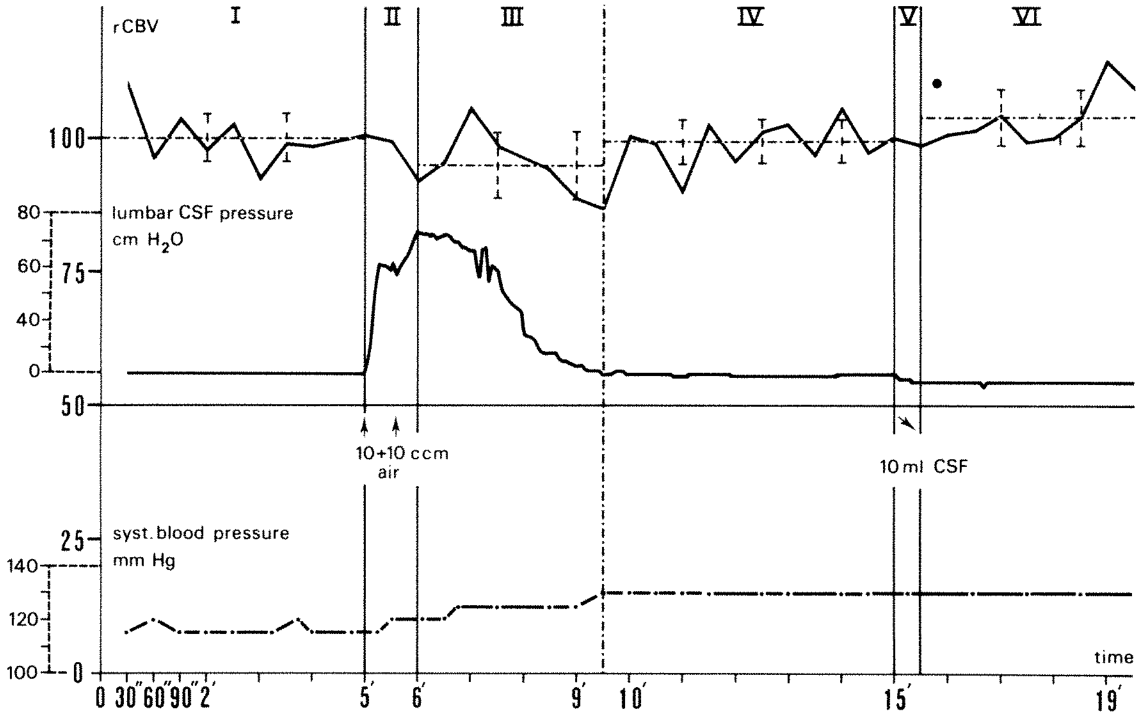

Fig. 4. Recordings of CBV, CSF pressure, and systolic blood pressure during pneumoencephalography in a representative case of Group A. Roman figures denote: I, initial phase before insufflation of air; II, insufflation period; III, period of CSF pressure restoration; IV, phase of restored CSF pressure; V, removal of CSF; and VI, period of CSF hypotension.

value occurred in all patients of Group A (Fig. 4, part IV). In contrast, patients with convexity block showed no CBV increase at all in the corresponding time intervals (Fig. 5, part IV). In two patients of Group B the decreased CBV level remained unchanged (which was followed up to one hour in one case), and in the last patient there was a further significant CBV decrease even after the original CSF pressure was re-established (Fig. 5, part IV). The significant differences in CBV between Group A and B after restoration of CSF pressure are shown as mean CBV values of all patients in Figure 6. In two of the normal patients a significant increase in CBV above the original 100 percent level, probably representing a reactive hyperemic response, was found after removal of an amount of CSF which equalled half the volume of the injected air (Fig. 4, part V; and VI).

DISCUSSION

The aim of the present study was to obtain a better knowledge of the pathophysiologic and volumetric interrelations which occur during pneumoencephalographic examinations. By analyzing some basic pathomechanic and functional aspects, a better understanding should be gained of the various types of complications resulting from pneumoencephalography.[24]

The dilatation of the ventricular system during fractional pneumoencephalography indicates that the injection of air acts as a space occupying lesion which is responsible for the increasing intracranial pressure (ICP). These effects of the injected air are likely to be accentuated due to the expansion of the air intracranially resulting from temperature differences between the examination room and the patient's body. Furthermore, it is well known that elevation of ICP causes impairment of cerebral blood

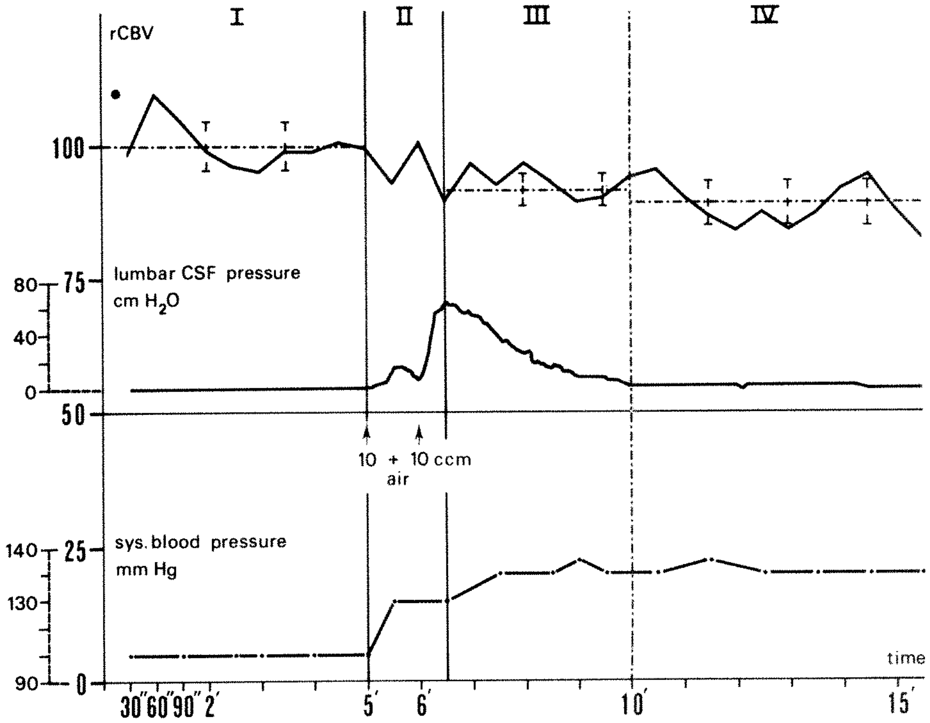

Fig. 5. Recordings of the same parameters in a representative case of Group B. Same symbols as in Figure 4.

flow (CBF) as shown by many authors using various methods such as cranial window studies,[13,32] angiographic circulation time,[8] radioisotope clearance,[3,9,38] magnetic flow meter,[7,15,27] and heat clearance.[17]

However, the reports on CSF pressure measurements during pneumoencephalography[1,11] have not dealt with the volumetric interactions related to changes of the vascular bed and produced by the reversible intracranial hypertension observed. In our examinations the regional cerebral blood volume (rCBV) was measured after intravenous injection of an intravascular nondiffusable gamma-emitting indicator ($^{113}\text{In}^{m}$). Animal experiments on dogs with skeletonized skulls[2] have shown that alterations in the extracerebral blood contents or in the systemic circulation act in such a degree and direction that they do not invalidate the conclusions reached. Moreover, the time resolution of the method is relatively high.[30]

During expansion of an intracranial mass lesion several processes occur simultaneously, and their nature may be studied using fractional pneumoencephalography as a simple experimental model. In normal patients each single amount of injected air is immediately and constantly followed by an elevation of CSF pressure with a concomitant rise of arterial blood pressure and bradycardia (Fig. 4; and 5, part II).[35] The intracranial compensatory mechanisms which re-establish the original CSF pressure after gas injections depend upon the interplay of several factors.

Important characteristics of each compliant system with respect to volumetric alterations are the elastic properties of this system which may be defined as the slope dP/dV (mm Hg/ml) of the CSF pressure-volume curve and then termed elastance.[26] Elastance as well as the inverse parameter compliance, dV/dP (ml/mm Hg), are thus a measure of the stiffness or rigidity of the system. Up to now, quantitative measurements of the compliance have been made only in dogs and have shown that the pressure-volume curve of the ventricular

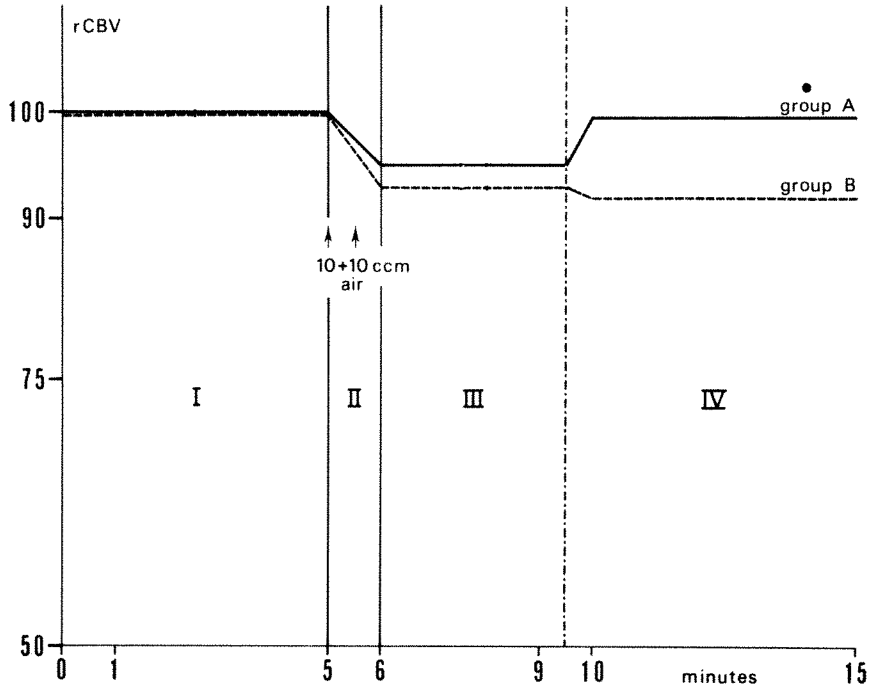

Fig. 6. Schematic drawing of the averaged CBV curves of Group A and B. The mean differences between values of period III and IV are statistically significant.

system has a modified exponential form.[23,26] Thus, the compliance of the brain is reduced with progressive ventricular enlargement, in accordance with the common neuroradiologic experience that the increase in ventricular size is greatest following the initial introduction of air and becomes relatively smaller upon additional air quantities. Regarding cranial and spinal components of the CSF pressure-volume curve in dogs, Löfgren and Zwetnow[26] found that 70 percent of the variation in volume within the system was related to responses in the spinal portion and 30 percent to those in the cranial portion. Therefore, the response of the biological system enclosed in the rigid container of bones (brain, vessels, CSF spaces, dural sheaths and extradural tissue) to a surplus of air will be determined by the interaction of the deformation properties of the system as a whole. However, the experiments in dogs involving elevated cephalic venous pressure, which caused higher pressure levels in the intracranial pressure-volume curve, indicate that the curve is related chiefly to changes in the vascular volume.[26] These authors have shown that intracranial volume decrease causes distention and a volume increase compression of the vascular bed, essentially in the venous portion.

In view of the immediate spatial adjustment to intracranial volume alterations caused by injections of air, displacement of CSF into the spinal dural sac and, in addition, a reciprocal change in the volume of the intracranial vascular bed have to be assumed and have recentlybeen studied in experiments on dogs.[2] In addition, there is evidence of a third compensatory mechanism regularly occurring in increased ICP. Investigations on the pacchionian granulations with regard to the pressure-outflow relationships in model experiments[36] as well as animal experiments with selective air-filling of the intra- and extraventricular subarachnoid CSF spaces[2] indicate an increased outflow rate of CSF into the sagittal sinus during elevated ICP. Such a mechanism also offers the best explanation for the difference in volumetric response between normal patients and patients with communicating hydrocephalus as observed in this investigation. In patients with convexity block there was always a more pronounced reduction of CBV in part III of the CBV curves (Fig. 5, part III) than in the normal group (Fig. 4, part III), despite the fact that in all patients the same total amount of air was injected (Fig. 6, part III). Although the number of examined patients is low our results show that in patients with convexity block the same surplus of insufflated air leads to a mean CBV decrease which is about 30 percent greater than in normals (Fig. 6). This implies that in normal patients, corresponding to parts II and III of the CBV curves, an additional ICP compensating mechanism exists which is missing or malfunctioning in patients with convexity block.

Still another regulatory CSF response, *i.e.*, concomitant decrease of CSF formation, may theoretically be considered under conditions of increased ICP during fractional pneumoencephalography. Deck *et al.*[5] in 1972, however, in their experimental studies have recently proved that air in the ventricles produced no significant change in the total formation of CSF. Hence an increased resistance to CSF outflow in the region of the absorption areas offers the best explanation for the findings in patients with convexity block. In accordance with these considerations no resultant return of CBV could be shown in patients with convexity block when the initial CSF pressure was re-established. In contrast to normal patients, those with convexity block showed the CBV level to remain at its reduced mean value or even below after restoration of the CSF pressure (Fig. 5, part III; and IV). It must be assumed that a continuing expansile force exists in patients with convexity block even in equilibrated CSF pressure stages, which compresses the venous system and is represented by the amount of CSF being not resorbed during the initial elevation of ICP. In preliminary experimental studies in dogs selective subarachnoid air-filling seems to produce an artificial convexity block, probably by the replacement of CSF by air in the extraventricular CSF pathways including the parasagittal resorption areas and thus increasing the outflow resistance to CSF.[2] In patients with convexity block, the resistance to CSF outflow may be a predominant factor in causing the compensatory greater reduction of CBV under the conditions of acute increased ICP in fractional pneumoencephalography.

The decrease in CBV should reflect a decrease in cerebral blood flow (CBF). According to Risberg *et al.*[30] and Smith *et al.*,[34] there is a linear relationship between regional CBV and CBF and a very high correlation between regional CBV and CBF changes ($r=.96$, $p<0.001$). This finding indicates that variations of rCBV normally are accompanied by proportional CBF changes and *vice versa*. The increase in cerebral circulation time (CCT) occuring with raised ICP[8] indicates, however, that the relationship between CBF and CBV is not linear in certain pathologic conditions. However, linear or non-linear, the correlation between CBF and CBV should remain positive. In this context, it is noteworthy that increase in CBF following shunting procedures for hydrocephalus occurs without the corresponding decrease in CCT[10] indicating that changes in CBF following changes in ventricular size are mainly brought about by a change in CBV.

Our findings during pneumoencephalography show that there is in fact a marked impact on CBV, resulting in a decrease which depends on the amount of injected air in the individual case (Fig. 6, part II; and III). The following considerations are based on the assumption of an intact autoregulation in our normal patients and of a positive correlation between CBF and rCBV. Therefore, in our encephalographic model it is assumed that CBF and CBV are reacting simultaneously and in a similar way. Thus CBF and CBV, respectively, are dependent on two main factors: the difference between mean systolic cerebral arterial pressure (CAP) and mean venous pressure (CVP), *i.e.*, the cerebral perfusion pressure (CPP), and the cerebral vascular resistance (CVR). CBV is normally regulated by alterations in the CVR, which in turn depends upon the diameter of the cerebral vessels, the ICP, and the blood viscosity. A volume increase in the intracranial CSF spaces, which always occurs in pneumoencephalography, results in a compression of the low pressure venous section[20,26,27,37] and may eventually compress the dural venous sinuses.[14,19] As ICP rises, however, CVP increases, and there is experimental evidence that the two pressures are nearly identical at all levels of increased ICP until the veins collapse.[33,37] Thus, ICP is often considered to be the outflow pressure when it is elevated:[20]

$$\mathrm{CPP} = \mathrm{CAP} - \mathrm{CVP}; \qquad \mathrm{CVP} = \mathrm{ICP}$$

$$\mathrm{CBV}\ (\mathrm{CBF}) = \frac{\mathrm{CPP}}{\mathrm{CVR}} \rightarrow \mathrm{CBV} = \frac{\mathrm{CAP} - \mathrm{ICP}}{\mathrm{CVR}}$$

According to this concept a rise in ICP causes compression of the cerebral venous system which in turn causes reduction of CPP and increase of CVR with resultant decrease of CBV.

It is not unlikely that the absence of restoration of CBV or even continuous CBV decrease after CSF pressure restoration may produce the clinical deterioration in some patients, and this occurs either because of impaired autoregulation or because of a low CBV level already existing at the beginning of the encephalographic procedure (Fig. 5, part IV). This is likely to be the fact in patients with low pressure hydrocephalus, who have a reduced CBV. During most pneumoencephalographic procedures, however, the injected air will reach the ventricular cavities as well as the subarachnoid spaces and constitute a blockage to CSF flow when reaching the basal cisterns. Therefore, an increase of outflow resistance to a certain degree must be taken into account in all fractional pneumoencephalographic examinations as a further cause of elevation of ICP with compensatory lowering of CBV. CBV measurements during ventriculography will help to distinguish and evaluate quantitatively the amount and value of each of these single factors as has been possible in dogs.[2] With regard to the pneumoencephalographic procedures, therefore removal of CSF (1) appears to be a reasonable approach in the acute stages of air-induced raised ICP especially in cases presenting with low pressure hydrocephalus, but (2) should be avoided when ICP is elevated before the examination. In that case, a large intracranial mass lesion has to be excluded by other methods.

Finally, we want to point out that even after compensation following the acute increased ICP related to all described mechanisms it cannot be said that the system as a whole has regained its original pressure characteristics. Despite the re-established CSF pressure levels in part IV of the CBV-curves of normal patients and those with convexity block persisting expansile forces must exist as represented by the encephalographically well-documented remaining ventricular enlargement. The total expansile force is a product of pressure times surface area,[12] which means that compression of the brain resulting from ventricular enlargement may be maintained at a lower pressure than would be required with normal sized ventricles. It is probable that this compression leads to obstruction of the blood vessels in which the pressure is low, such as veins.[9] That this is true can be shown in our examinations by the persistently lowered CBV in patients with convexity block. This was followed up to one hour in one case. Furthermore, this assumption is supported by the reactive hyperemic response which always occurred in normal patients after withdrawal of CSF in an amount corresponding to half the quantity of injected air (Fig. 4, part VI).

Therefore, we believe that the combination of fractional pneumoencephalography and CBV measurements can be taken as an experimental model to study and evaluate the pathophysiologic volumetric interactions of acute hydrocephalus as well as those of low pressure hydrocephalus. It appears from the present study that acute hydrocephalus, with decreased CPP and altered CSF dynamics, adversely affects cerebral circulation and CBV and that early recognition and prompt relief of hydrocephalus are important to the patient. Furthermore the relationship between CBV and ventricular dilatation in fractional pneumoencephalography may help to differentiate at least certain types of cerebral atrophy from hydrocephalus and serve as a guide in the selection of cases for operation.

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FRONTAL VENTRICULAR DIMENSIONS ON NORMAL COMPUTED TOMOGRAPHY

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ABSTRACT:

The computerized axial tomographic examinations of 200 normal patients and volunteers between the ages of ten to 81 years were evaluated. Determination of the ratio between the width of the brain and a dimension representing the distance between the outer borders of the lateral ventricles was made at two levels. This ratio, the cerebroventricular index, seems to be a reliable indicator of ventricular size. The standards vary with the age of the patient.

ALTHOUGH the computerized axial tomographic (CT) scan of the brain is accepted as a valuable procedure for the evaluation of cerebral ventricular size, the normal range of ventricular size as seen on the CT scan has not been established in the literature. The recognition of mild or moderate ventricular dilatation or reduction on the CT scan has been based on experience, and the lack of any quantitative data has led to some controversy. For the purpose of establishing quantitative criteria of ventricular size for comparative diagnoses, 200 normal CT scans and 65 abnornal CT scans were studied.

The frontal ventricular dimensions as measured by a Vanguard Motion Analyzer are correlated with age and provided in this paper.

MATERIAL AND METHOD

From the University of Iowa Hospital's computer memory bank containing the CT scan data of over 1,500 patients, the investigators screened and assembled the data for normal sized ventricles and various types of abnormalities. (The present report emphasizes the study of normal ventricles.) The normal CT scans were derived from 180 patients who were ultimately considered neurologically normal, and from 20 normal volunteers. These 200 normal individuals included 97 males and 103 females with an age range from ten to 81 years.

CT scans were performed in a standard fashion[1,2,3] with an approximate 15 degree tilt from the canthomeatal line. In all cases 2A and 2B images were utilized because they provided the best images of the frontal horn; 2B images frequently showed the maximum bicaudate diameter to best advantage. Initially, the measurements were derived in the traditional manner from the original Polaroid images utilizing a ruler. In order to minimize the potential measurement error, the investigators subsequently transposed all the tomographic Polaroid images on a roll of 35 millimeter film and then projected each film frame with proper magnification on the screen of a Vanguard Motion Analyzer. This is a precision reader whose accuracy is better than 0.1 percent in linear measurements. The dimensions of each subject measured on the analyzer screen were automatically digitized and transcribed on an IBM card through key punching. In each case, the following dimensions were measured:

A. The maximum bifrontal diameter: the transverse distance defined by a line connecting the two anterior corners of the frontal horn (Fig. 1).
B. The first transverse dimension of the brain (brain width): the distance measured along the line of the bifrontal diameter from the right to the left cortical surfaces (Fig. 1).

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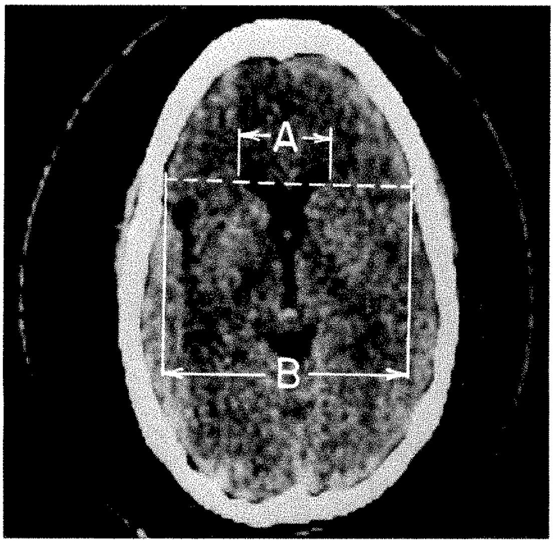

FIG. 1. Illustration of measurements A and B, respectively, the maximum bifrontal distance and the first transverse dimension of the brain.

C. The maximum bicaudate diameter—the transverse dimension through the body of the frontal horn measured along a line drawn from the mid-portion of the head of one caudate nucleus to the other (Fig. 2).

D. The second transverse dimension of the brain (brain width)—the distance measured along a line extending from the right to the left cortical surfaces through the line of the bicaudate diameter (Fig. 2).

The A and C measurements provide two characteristic dimensions of the frontal ventricular horn, whereas B and D measurements reflect brain size. All measurements were made in millimeters. However, the A and C measurements were divided by two characteristic dimensions of the brain B and D, respectively, so as to ensure the independence of the results of the present study from particular scale factors utilized in sizing up the CT scan images as well as from the units of measurement employed; furthermore, the influence of variations in the size of the frontal horns due to anthropometric differences in normal individuals is minimized.

The ratios obtained are dimensionless and may be called the first (A/B) and second (C/D) cerebroventricular index (CVI) of the frontal horns. The first ratio multiplied by 100 gives the percent of the maximum bifrontal diameter (A) to brain width (B); and the second ratio (C/D) multiplied by 100 expresses that of the bicaudate diameter (C) to brain width (D). The results of the present study are therefore presented in terms of the percentage of the maximum bifrontal diameter (A) to brain width (B), and the percentage of the bicaudate diameter (C) to brain width (D).

RESULTS

These percentages, $(A/B)\times 100$ and $(C/D)\times 100$, are plotted with respect to age in Figures 3 and 4, respectively. A line representing a least square fit to all the points is drawn through each graph. Table I provides the mean, standard deviation, maximum, and minimum values of these percentages for the 200 normals investigated. As an illustration of the use of Table I as a standard reference, the results of the analysis of a group of 65 abnormals with ventricular dilatation from various causes are presented in Table II and may be com-

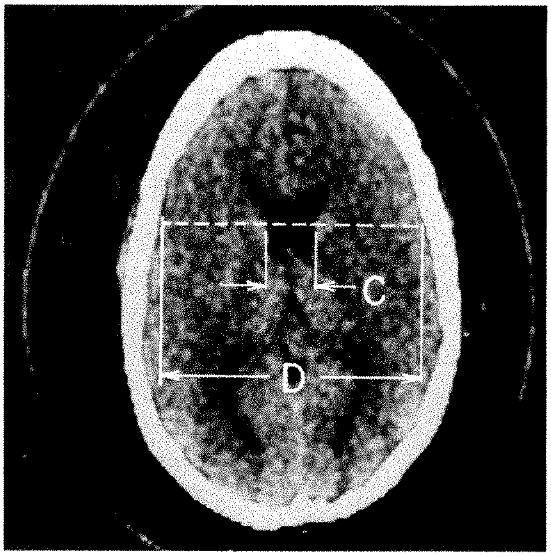

FIG. 2. Illustration of measurements C and D, respectively, the maximum bicaudate diameter and the second transverse dimension of the brain.

pared with those of normals. As a guide for comparative diagnosis, this study establishes that the maximum bifrontal diameter of the normal frontal ventricle varies from 19 percent to 39 percent of brain width B and its mean value for all ages is 31 percent with a standard deviation of four percent. The maximum bicaudate diameter of the normal frontal ventricle varies from eight to 23 percent of brain width D and its mean value for all ages is 15 percent with a standard deviation of three percent. Figures 3 and 4 also reveal the interesting tendency of the maximum bifrontal diameter of the normal frontal ventricle to increase with age, from approximately 28 percent of brain width B at the age of 15 years to 31 percent at the age of 70 years. The same is true for the bicaudate diameter of the normal frontal ventricle which measures approximately 13 percent of brain width D at the age of 15 years and 17 percent of brain width at the age of 70 years. The group of hydrocephalic patients which is presented only for purposes of comparison warrants the following observations: the mean bifrontal and bicaudate cerebroventricular indices in this group are increased approximately one and one-half to two times respectively, in comparison to the normal group.

DISCUSSION

Estimation of ventricular size can be accomplished in most instances by relying on the training and experience of the radiologist. Yet, the relative newness of CT scanning has not permitted the acquisition of extensive experience, and quantitative criteria are likely to prove helpful in some borderline cases: such criteria may also serve as objective standards against which one may test the diagnostic reliability which is presently based on reconditioning acquired in other techniques such as pneumoencephalography.

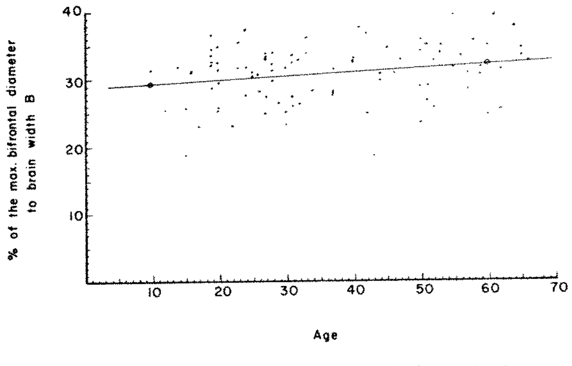

Fig. 3. Percentage of the maximum bifrontal diameter to brain width B *versus* age for 100 normal individuals.

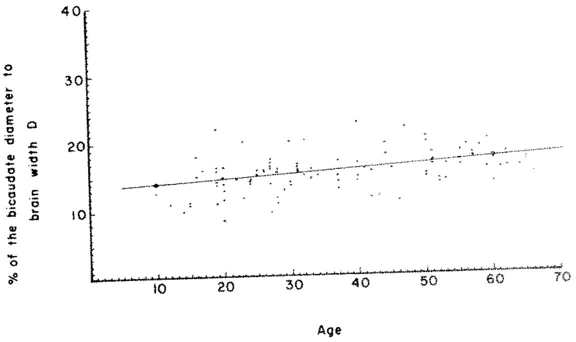

Fig. 4. Percentage of the maximum bicaudate diameter to brain width D *versus* age for 100 normal individuals.

The cerebroventricular index derived from the more dorsal portion of the frontal horns, *i.e.*, the bicaudate CVI, appears to be more sensitive than the bifrontal CVI in the detection of changes in ventricular size. Notwithstanding this expected observation, there is some overlap of the normal distribution curves derived from the normal and hydrocephalic groups of patients in this study. The mean and standard deviations derived from the two bell shaped curves characterizing the two patient groups are such that slightly less than five percent (4.55 percent) of each group's constituents are sufficiently remote from the mean to intersect with members of the other group; this measure may be held to reflect a minimum theoretical false positive or false negative rate respectively.

The principal objective of this brief report is to present the quantitative data pertaining to the size of the normal ventricular system as reported on CT scans. The

TABLE I

CEREBROVENTRICULAR INDICES (CVI) OF BIFRONTAL AND BICAUDATE DIAMETERS OF 200 NORMAL CT SCANS

	Mean (Percent)	Standard Deviation (Percent)	Minimum Value (Percent)	Maximum Value (Percent)
CVI of bifrontal diameter (A/B)×100	31.1	3.7	18.5	39.3
CVI of bicaudate diameter (C/D)×100	15.4	2.8	8.1	23.2

TABLE II

CEREBROVENTRICULAR INDICES (CVI) OF BIFRONTAL AND BICAUDATE DIAMETERS OF 65 ABNORMALS WITH VENTRICULAR DILATATION

	Mean (Percent)	Standard Deviation (Percent)	Minimum Value (Percent)	Maximum Value (Percent)
CVI of bifrontal diameter (A/B)×100	44.8	7.8	33.8	77.8
CVI of bicaudate diameter (C/D)×100	29.3	5.7	19.1	45.9

problems posed by alterations in size due to various pathologic processes will be considered in subsequent communications.

SUMMARY

Utilizing the Vanguard Motion Analyzer with computer analysis, 200 normal and 65 abnormal CT scans of the brain were studied. Normal ranges of bifrontal and bicaudate diameters of the frontal horn of the lateral ventricle, and ratios of these distances to the brain widths on the same levels were determined. The results are presented graphically.

It is suggested that a maximum bicaudate diameter greater than 22 percent or less than eight percent, or a maximum frontal diameter greater than 40 percent or less than 18 percent, of the widths of the brain on the corresponding levels are highly suspicious of abnormal ventricles.

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BRONCHOGRAPHY IN PATIENTS WITH HEMOPTYSIS*

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ABSTRACT:

Retrospective analysis of 196 cases suggests that bronchography has limited value in the evaluation of hemoptysis. Most patients with a single episode of hemoptysis and normal plain chest roentgenographic and bronchoscopic findings do not require bronchographic examination. Advances in cytologic and biopsy procedures (fiberoptic bronchoscopy, bronchial brushing, needle aspiration) have largely replaced the usefulness of bronchography even when the plain chest roentgenogram is abnormal.

THE evaluation of hemoptysis is a common clinical problem. Although the etiology may be readily apparent, many patients with this symptom present a difficult diagnostic problem. Bronchography has been commonly used in the past to evaluate these problem cases.[1]

This paper analyzes the results of 196 bronchograms performed in patients who had hemoptysis.

MATERIAL

The case records and roentgenograms of 463 adult in-patients who had bronchograms over a four year period at the Barnes Hospital—Washington University Medical Center were evaluated. Over 90 percent of these patients were referred from the thoracic surgery division for evaluation. In 196 of these patients, hemoptysis was a significant complaint. Each of these patients first had a history and physical examination, a chest roentgenogram, bronchoscopy, and, when appropriate sputum cytology. Generally, because the results of these examinations were inconclusive, a bronchogram was performed to elicit the cause of the hemoptysis.

METHOD

All of the bronchograms were performed with oily Dionosil through a catheter introduced *via* the transcricothyroid membrane approach using a modified Seldinger technique.[9] Bilateral, unilateral, or selective studies were performed in appropriate cases depending on the clinical situation, particularly the findings on the plain chest roentgenogram.

RESULTS

The bronchographic findings in the patients with hemoptysis are summarized in Table I.

Normal plain chest roentgenogram: In the 92 patients with normal plain chest roentgenograms, bronchography disclosed two cases of localized bronchiectasis and two cases of benign broncho-occlusive disease (presumably due to old healed granulomatous disease) (4.5 percent). Thirty-three patients (36 percent) had bronchographic findings consistent with chronic bronchitis.[8] No case of lung carcinoma undetected by plain chest roentgenography or bronchoscopy was disclosed by bronchography.

Abnormal plain chest roentgenogram: In six patients with chronic consolidation, volume loss, or both, in a lobe or segment detected on the plain chest roentgenogram, bronchography was of value in excluding broncho-occlusive disease, thus for practical purposes ruling out a central carcinoma as a diagnostic possibility.

Bronchography confirmed broncho-occlusive disease suggested by plain chest roentgenograms or bronchoscopy in 39 patients. The five cases due to benign

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TABLE I

BRONCHOGRAPHIC FINDINGS IN PATIENTS WITH HEMOPTYSIS

A. Essentially Normal Plain Chest Roentgenogram	
Normal bronchogram	55
Chronic bronchitis	33
Broncho-occlusive disease	2
Localized bronchiectasis	2
	92
B. Abnormal Plain Chest Roentgenogram	
Normal bronchogram	5
Localized bronchial irregularities without broncho-occlusive disease	6
Broncho-occlusive disease	39
Broncholithiasis	3
Bronchiectasis	12
Chronic bronchitis	39
	104

broncho-occlusive disease were indistinguishable on roentgenologic grounds from the 34 patients subsequently proved to have neoplasm as the cause of the bronchial occlusion. Bronchial brushing, which was combined with bronchographic examination in the majority of cases, was able to furnish a definitive diagnosis in 15 of 23 cases of carcinoma and in one case of tuberculous bronchitis.

A diagnosis of broncholithiasis was made in three patients who on bronchography had a localized bronchial abnormality adjacent to an area of calcification.

Bronchography established the diagnosis of bronchiectasis in twelve patients with abnormal plain chest roentgenographic findings. In five of the twelve a diagnosis of bronchiectasis was suggested by the plain chest roentgenograms.

It is of interest that the quantity of hemoptysis did not correlate with any specific diagnosis in our 196 patients (Table II). No patient in our series either died of the hemoptysis or required blood transfusions. However, this report is not a comprehensive study of patients with hemoptysis, but includes only those patients who underwent both bronchoscopy and bronchography. Patients with life threatening hemoptysis would not ordinarily have bronchography. In these patients bronchoscopy and sometimes a plain chest roentgenogram often will localize the bleeding site and allow proper surgical treatment.

DISCUSSION

Hemoptysis is a distressing problem to both patient and clinician since it may be the presenting manifestation of significant pulmonary disease. Many authors advocate bronchography as part of the routine evaluation of patients with hemoptysis.[2,3] In a recent review of bronchography by the American College of Chest Physicians, hemoptysis was the second most common reason for performing bronchography.[1] Yet our results indicate that bronchography has limited use in the evaluation of hemoptysis, especially when the patient has a normal plain chest roentgenogram.

In patients with a normal plain chest roentgenogram, bronchography only rarely discloses an abnormality likely to alter clinical management. These findings suggest that a conservative "wait-and-see" attitude should prevail in the patient with one or two closely related episodes of hemoptysis in whom the plain chest roentgenogram and bronchoscopy are negative. Bronchography might be of value if the fiberoptic bronchoscope demonstrates a suspicious lesion or blood coming from a specific segmental bronchus. It is unlikely that a significant lesion will be missed in a patient with a normal plain chest roentgenogram due to the increased range of visability added by fiberoptic bronchoscopy. Reinforcing our contention are the results from a previous study which evaluated 481 patients with hemoptysis, separating them into those who had a normal and those who had abnormal chest roentgenograms. In a three year follow-up of the patients who originally had a normal chest roentgenogram, only one significant disease process was discovered.[6]

When the diagnosis is not obvious, clinical

Table II

CORRELATION OF HEMOPTYSIS QUANTITY AND FINAL CLINICAL DIAGNOSIS

Final Diagnosis in Patients with Hemoptysis	Massive*	Frank†	Trace‡	Not Recorded	Total
Unknown cause	8	20	15	17	60
Bronchitis	18	24	21	9	72
Lung cancer	1	6	15	12	34
Bronchiectasis	3	2	6	3	14
Chronic pneumonia (including the right middle lobe syndrome and its variants)	1	2	4	1	8
Broncholithiasis	1	0	1	1	3
Active pneumonia	0	1	1	0	2
Active tuberculosis	0	1	0	1	2
Pulmonary embolus	0	0	1	0	1
Total	32	56	64	44	196

* Massive if more than one cup in a single day.

† Frank if the patient had at least a mouthful of blood or large clots.

‡ Trace if less than a mouthful of blood, usually only streaking of the sputum.

follow-up will usually be revealing without the need for bronchography. Should the hemoptysis persist, then bronchography may be considered. It is possible that a patient with a surgically curable problem not appreciated on history, physical, plain chest roentgenographic study, or bronchoscopy could develop fatal hemoptysis. However, from our experience, this is rare.

Although bronchography disclosed abnormalities in the majority of patients with abnormal plain chest roentgenographic findings, it was not usually of significant value to guide patient management. Exclusion of broncho-occlusive disease and the definitive diagnosis of bronchiectasis were its outstanding contributions.

In the patients with hemoptysis in whom a suspicious mass lesion was seen on the plain chest roentgenogram, bronchography was useful in determining the presence or absence of bronchial occlusion or filling defects beyond the reach of the bronchoscope. In our experience it was most helpful when patent bronchi were seen throughout the lesion, for the absence of broncho-occlusive disease is good evidence that neoplasm is not the cause of the abnormal infiltrate. Thus in the patient with minor hemoptysis in whom the plain chest roentgenogram demonstrates a localized area of consolidation, thoracotomy usually can be averted if the bronchogram demonstrates patent bronchi, and fiberoptic bronchoscopy, bronchial brushing, and sometimes needle aspiration biopsy are negative. The lesion would be presumed to be due to chronic organizing pneumonia.

When broncho-occlusive disease was discovered, however, bronchography alone was not sufficiently helpful in distinguishing the benign inflammatory form from neoplasm. The diagnosis of neoplasm by bronchography always remained inferential, whereas cytologic techniques such as bronchial brushing or needle aspiration often achieved definitive diagnosis, permitting the direct institution of treatment, be it surgery or radiation therapy.[4,7]

While plain chest roentgenograms are usually abnormal in bronchiectasis[5] the findings are often non-specific and only bronchography is capable of definitively determining the presence and extent of bronchiectasis. Some cases of broncholithiasis can also be best, and occasionally only, diagnosed by this method. The finding of extrinsic narrowing of a major bronchus along with filling of crowded peripheral bronchi, sometimes in association with mild bronchiectasis, permitted the definitive diagnosis of the middle lobe syndrome or its variants in several instances.

The exact significance of the bronchographic findings consistent with chronic bronchitis is uncertain since a similar proportion of patients without hemoptysis who underwent bronchography had similar findings. We were unable to correlate the presence or severity of these findings with hemoptysis.

In our series the incidence of broncholithiasis may have been underestimated. St. Louis is an endemic area of histoplasmosis, and the majority of adult chest roentgenograms demonstrate hilar and perihilar calcifications. Patients with these calcifications are not included in our "abnormal" plain film classification. In some cases these calcifications may have impinged upon or eroded into the bronchial tree causing hemoptysis. While a change in location or disappearance of a calcification may be a clue to such an event, this is rarely seen. It is also unusual for patients to report having coughed up gravel or similar material. Occasionally the bronchogram will suggest this etiology of hemoptysis when localized bronchial irregularity is seen adjacent to the calcific focus. Probably some of our idiopathic cases and some classified as bronchitis were due to broncholithiasis.

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ISOLATED ROTATORY SUBLUXATION OF THE CARPAL NAVICULAR*

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ABSTRACT:

Rotatory subluxation of the carpal navicular can cause wrist pain and may lead to severe and disabling degenerative changes. Correct diagnosis depends on recognition of the typical roentgenographic signs.

Sixteen patients with neither rheumatoid arthritis nor a lunate or a perilunate dislocation had rotatory subluxation in nineteen wrists. Many had only vague or remote histories of trauma. There were a navicular-lunate gap in all nineteen wrists, and foreshortening of the navicular in sixteen wrists, usually with a ring sign.

The abnormalities were best demonstrated on well-centered posteroanterior roentgenograms of the wrist with the hand in slight radial deviation. In two patients, wrist arthrography demonstrated abnormal communication between radiocarpal and intercarpal joints.

ROTATORY subluxation of the carpal navicular can occur when the navicular-lunate ligament is torn during a lunate or a perilunate carpal dislocation (Fig. 1), or is destroyed by the granulation tissue of rheumatoid arthritis (Fig. 2). The disruption of this ligament permits posterior (dorsal) rotation of the proximal pole of the navicular. In rheumatoid arthritis, this malposition is only one feature of the total disorganization of the carpus that can occur.[4] Persistent or recurrent rotatory navicular subluxation following reduction of lunate or perilunate carpal dislocations may cause persistent pain and limitation of wrist motion.[8,12,13]

It is important to realize that this same rotatory subluxation may be found in patients with neither a previous dislocation nor inflammatory arthritis.[2,5,6,9,11–14] Such patients are the subject of the present study. Patients with this isolated abnormality may be evaluated by numerous physicians before the correct diagnosis is made. Although the diagnosis is made roentgenologically rather than clinically, only a single case report has been published in the radiologic literature.[5] The present report is intended to familiarize radiologists with characteristic roentgenographic findings of rotatory subluxation of the carpal navicular, and with the techniques of obtaining appropriate, diagnostic roentgenograms. It is hoped that this will lead to earlier diagnosis and treatment, and prevent serious late disabilities in patients with this condition.

MATERIAL

The clinical records and roentgenograms of sixteen patients with rotatory subluxation of the carpal navicular were reviewed (Table I). Three patients (Cases III; IX; and XIV) had the condition in both wrists, so there were nineteen wrists involved. None of these patients had rheumatoid arthritis and none had sustained a lunate or a perilunate dislocation. The severity of the symptoms and disability varied widely. The most striking aspect of many histories was the delay in diagnosis. Many patients had consulted several physicians and had

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* Presented at the Seventy-sixth Annual Meeting of the American Roentgen Ray Society, Atlanta, Georgia, September 30–October 3, 1975.

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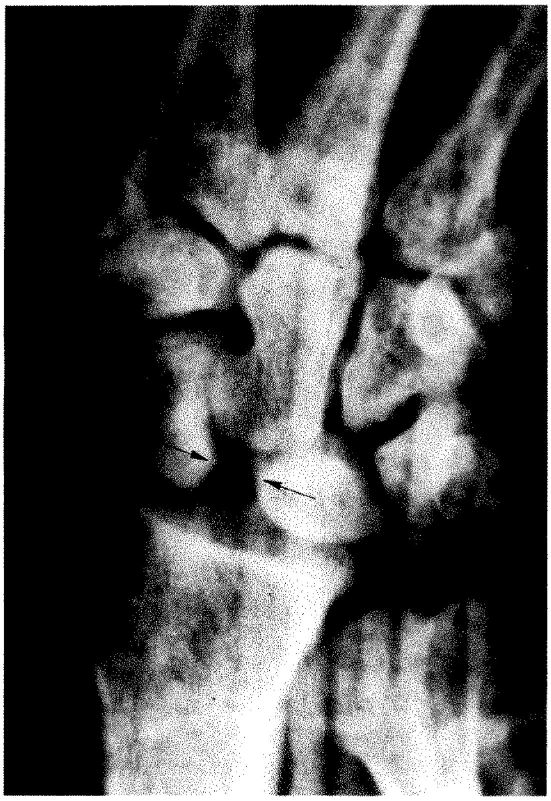

Fig. 1. A young man sustained a perilunate carpal dislocation. Roentgenogram made through plaster after closed reduction shows rotatory subluxation of the navicular with navicular-lunate gap (arrows) and foreshortening of the navicular.

been followed for some time before the diagnosis was made. One patient had consulted twelve orthopedic surgeons over a two year period.

In thirteen of the involved wrists, there was a definite history of trauma. In six instances, the patient had fallen on the wrist or hand. In three, there was a twisting injury during use of the hand. One patient, while playing baseball, collided with another player, another was kicked by a cow, a third had "fractured" her navicular in a fall two years earlier, and a fourth patient had "fractured his wrist" thirty-six years earlier. Two patients thought they had previously injured the wrist but could not recall details. In four cases, the patient could recall no trauma, although one patient had undergone surgical carpal tunnel release three months previously.

All nineteen involved wrists were painful. In five instances, the patient complained of weakness, or inability to grip well with the involved hand. Two patients had symptoms of "clicking" or "snapping." On physical examination, the orthopedic surgeon found some limitation of motion in four wrists, tenderness in four wrists, and swelling in two wrists.

Eight wrists did not cause severe problems and received no treatment or were managed by restriction of activities and mild analgesics. In two cases, external wrist support was prescribed. Six wrists required surgery. In two, open reduction with soft tissue repair and temporary Kirschner wire fixation was performed. In two other instances, open reduction and

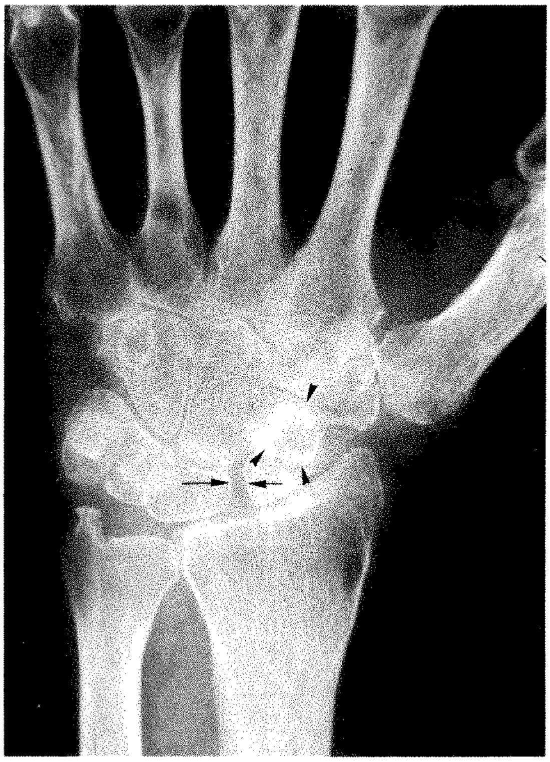

Fig. 2. A 67 year old woman with severe rheumatoid arthritis. There are erosions and periarticular demineralization. Navicular-lunate gap (arrows) and foreshortening of the navicular with a ring sign (arrowheads) indicate rotatory subluxation of the navicular.

Table I

19 INSTANCES OF ROTATORY SUBLUXATION IN 16 PATIENTS

Patient	Clinical Data		History of Trauma at Onset	Roentgenographic Findings			Treatment
	Wrist Involved	Symptoms and Signs		Navicular Lunate Gap	Navicular Ring Sign	Degenerative Changes	
1. A.L.	Left	Pain and limited motion 1 mo.	Fell on wrist	+	+	−	Conservative
2. A.B.	Right	Intermittent pain 4 yr.	None recalled	+	+	+	None
3. S.F.	Left	Pain, limited motion, tenderness	"Snapping" injury 2 yrs. before	+	+	+	External support
	Right	Pain 1 yr.	"Rotational" injury	+	+	−	None
4. J.Me.	Left	Pain, "snapping" 2 yr.	Collided with another player in baseball game	+	+	−	Open reduction and internal fixation
5. J.Mo.	Right	Pain	Poorly recalled injury 14 yr. before	+	+	+	Conservative
6. R.R.	Right	Pain, weakness	"Fractured wrist" 36 yr. before	+	+	−	Proximal carpal row resection
7. I.G.	Right	Pain 3 mo. when playing tennis	None recalled	+	+	−	No follow-up
8. G.P.	Right	Pain, swelling, tenderness	Vague recent injury	+	+	−	Open reduction and internal fixation. Subsequently required proximal carpal row resection
9. N.K.	Right	Pain, swelling, weakness, limited motion	Fell from train	+	−	−	Open reduction and internal fixation
10. M.Pu.	Left	Pain 2 yr.	"Fractured navicular" 2 yr. before	+	+	+	Proximal carpal row resection
	Right	Pain, weakness	Slipped in bath tub	+	+	+	Open reduction and internal fixation Subsequently required proximal carpal row resection
11. M.R.	Right	Mild pain	None recalled	+	+	+	No follow-up
12. R.F.	Right	Pain, clicking, tenderness 1 yr.	Fell on wrist	+	−	+	Conservative
13. M.Pa.	Right	Pain 1 yr.	"Twisted" wrist	+	−	+	No follow-up
14. L.W.	Right	Pain playing tennis	Jumped from burning house 2½ yr. before	+	+	−	Conservative
15. F.W.	Left	Pain, weakness	None recalled. Surgical carpal tunnel release 3 mo. before	+	+	+	None
	Right	Pain, weakness, worse than left	Kicked by cow following carpal tunnel release 3 mo. before	+	+	+	Leather gauntlet
16. B.H.	Right	Pain, tenderness 2 yr.	Fell on wrist	+	+	+	Conservative

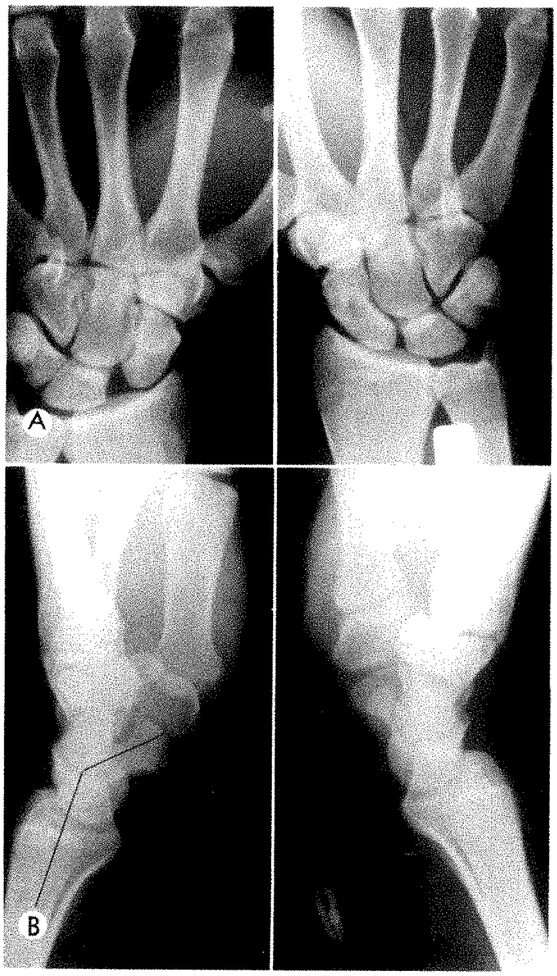

FIG. 3. Case IV. (*A*) The left wrist shows an abnormal navicular-lunate gap and foreshortened navicular with a ring sign. Compare with the normal right wrist. (*B*) Lateral view of the wrist shows a decreased volar radio-navicular angle on the left.

repair were unsuccessful, and proximal carpal row resection was later performed. In the remaining two, proximal carpal row resection was done as the initial procedure. Three patients were lost to follow-up.

ROENTGENOGRAPHIC FINDINGS

Three roentgenologic findings of rotatory subluxation of the navicular have been described. The first is an increased distance, or "gap" between the adjacent cortices of the carpal navicular and the lunate on the frontal roentgenogram (Fig. 3*A*; 4; and 5). This was present on at least one roentgenogram in all nineteen wrists with rotatory subluxation. In one wrist, the gap was partially filled by the proximally displaced capitate (Case XI, Fig. 7).

A ring sign has also been described.[5] This is simply the cortex of the distal pole of the navicular seen end on because the dorsal rotation of the proximal pole brings the distal pole more parallel to the roentgen-ray beam. Because of this abnormal position, the navicular also appears foreshortened on the frontal roentgenogram (Fig. 3*A*; 4; and 5). This ring sign and accompanying foreshortened appearance of the navicular were found on at least one roentgenogram of sixteen wrists. In one wrist, the navicular was foreshortened but a definite distal cortical ring could not be

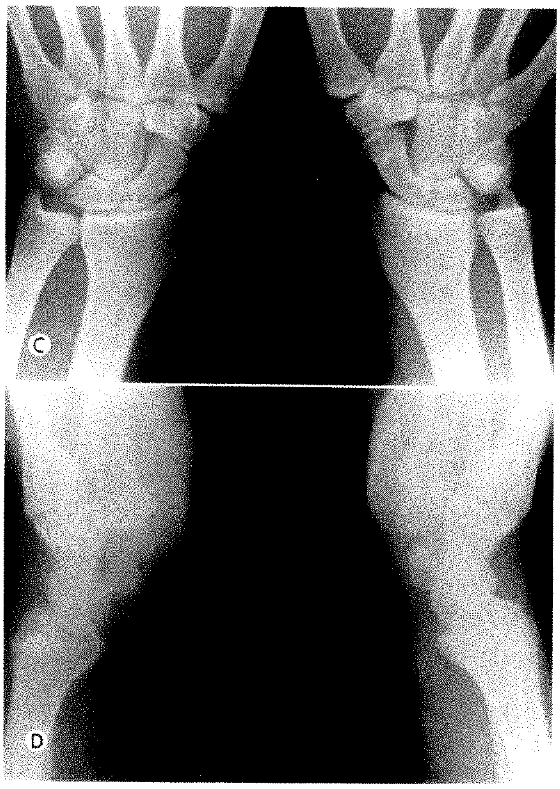

FIG. 3. (*C* and *D*) Seven months after open reduction of the navicular and repair of the ligaments, the left wrist appears essentially normal on the posteroanterior roentgenogram. Lateral views show restoration of the left navicular to a more normal position.

seen. Two others showed neither a ring nor foreshortening.

The third finding is an abnormal position of the navicular with respect to the radius on the lateral roentgenogram. A radio-navicular angle may be measured on the volar aspect of the wrist between a line drawn along the long axis of the navicular and one along the radial shaft (Fig. 3*B*). An abnormally small angle is said to indicate rotatory subluxation.[5] In this case material, measurement of this angle was unreliable. In only three wrists was the navicular position obviously abnormal with respect to the radius on the lateral view. In three others, the navicular appeared abnormal when compared with the opposite one. In one case, the lateral view was unsatisfactory, and this finding could not be evaluated. In twelve wrists, the appearance was normal or equivocal. The radio-navicular angle was measured on thirty-six roentgenograms of wrists with rotatory subluxation taken at various times. The average was one hundred and twenty-seven degrees, with values ranging from seventy-seven to one hundred and fifty-five degrees. In eight roentgenograms of normal opposite wrists, the average measurement was one hundred and fifty degrees with a range from seventy-seven to one hundred and eighty-seven degrees.

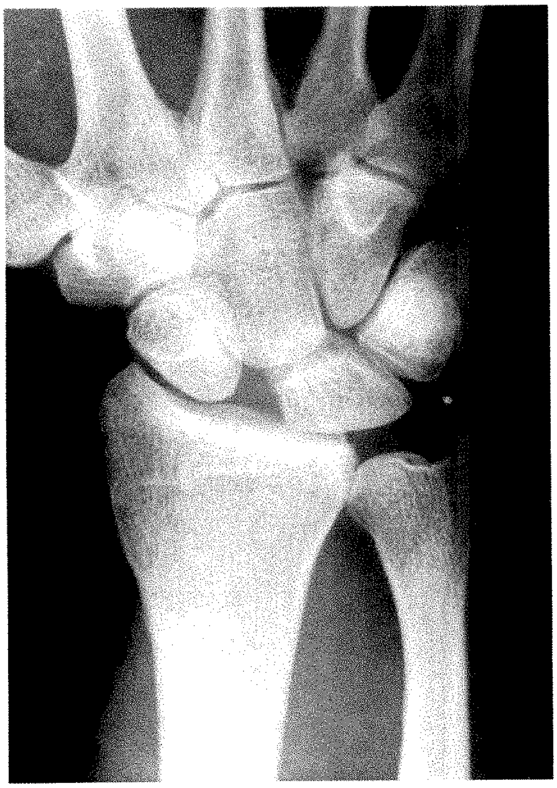

Fig. 4. Case vii. Navicular-lunate gap and foreshortened navicular with a ring sign. The wrist is in slight radial deviation (lunate displaced over ulna): There is good posteroanterior positioning (radius and ulna do not overlap significantly).

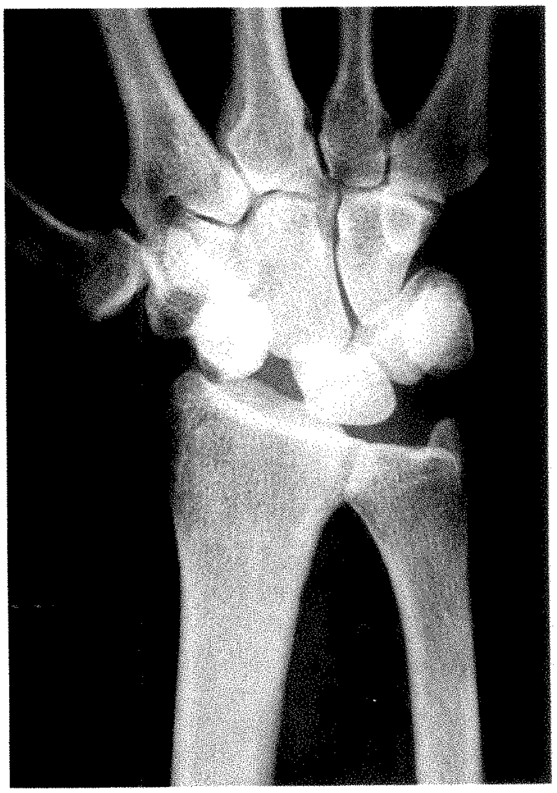

Fig. 5. Case x. Large navicular-lunate gap and markedly foreshortened navicular with a ring sign.

Articular cartilage narrowing and osteophyte formation were found in eleven wrists (Fig. 6; and 7). These changes involved the radiocarpal joint almost exclusively.

In two patients, wrist arthrograms were performed (Fig. 8; and 9). Both showed an abnormal communication between the

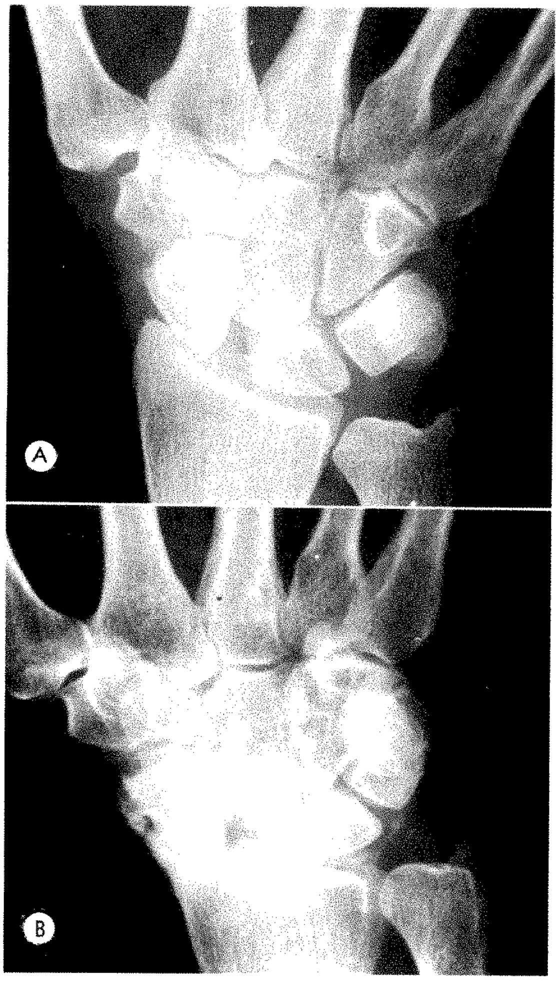

Fig. 6. Case v. (*A*) Posteroanterior roentgenogram with well-defined navicular-lunate gap and foreshortening of the navicular with a ring sign. (*B*) Three years later there are severe degenerative changes. The capitate is partly displaced proximally into the navicular-lunate gap.

injected radiocarpal joint space and the inter-carpal joints.

DISCUSSION

Rotatory subluxation of the carpal navicular should be considered whenever a patient complains of wrist pain, whether or not there is a definite history of trauma. This is especially true if the patient has inability to grip forcefully because of pain or weakness. In general, however, the history and clinical findings are nonspecific. The diagnosis should be made roentgenographically on the frontal film of the properly positioned wrist.

The abnormally rotated position of the navicular causes the wide navicular-lunate gap and foreshortening of the navicular, often with a ring sign. Two aspects of wrist positioning critically affect detection of these signs. The first is the accentuation of the abnormal position of the navicular by radial deviation of the hand. Often a neutral position is adequate, but ulnar deviation may obscure the findings. There is confusion in the literature with respect to this point. Thompson *et al.*[12] and Tullos *et al.*[13] recommend a supination view of the wrist, suggesting that it may be the only view demonstrating the navicular-lunate gap. Thompson *et al.*[12] also state that only roentgenograms with radial deviation of the

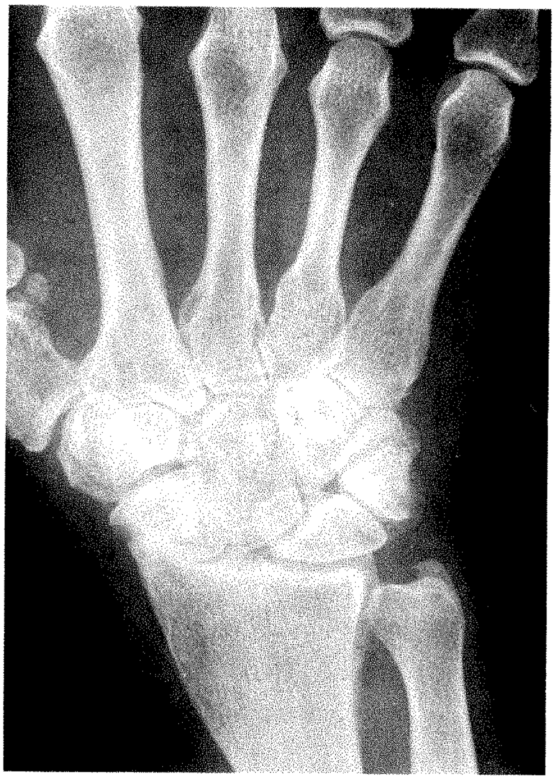

Fig. 7. Case xi. Wrist roentgenogram on initial presentation. The capitate is displaced proximally into the navicular-lunate gap. The navicular is foreshortened, with a ring sign. There are advanced radiocarpal degenerative changes.

hand show the loss of height of the navicular. The findings of the present study further emphasize the importance of radial deviation. This was a retrospective study, and multiple views were not always available. There were ten wrists in which both pronation and supination roentgenograms were available. In five cases the abnormalities were more evident on the supination view, but in every one of these there was also greater radial deviation on the supination view (Fig. 10). In the five wrists which showed about the same severity of gap and foreshortening on pronation and supination, there was either no significant difference with regard to radial or ulnar deviation, or there were differences in the posteroanterior positioning. Accentuation of the rotatory subluxation by radial deviation conflicts with the findings of Arkless,[1] who observed widening of the navicular-lunate gap on ulnar deviation during cineradiography of three of five wrists with rotatory subluxation of the navicular. In the other two wrists, he described excessive motion of the proximal navicular pole. England[6] performed cineradiography of one such wrist and found subluxation of the navicular in pronation and radial deviation, and relocation in dorsiflexion, supination, or ulnar deviation.

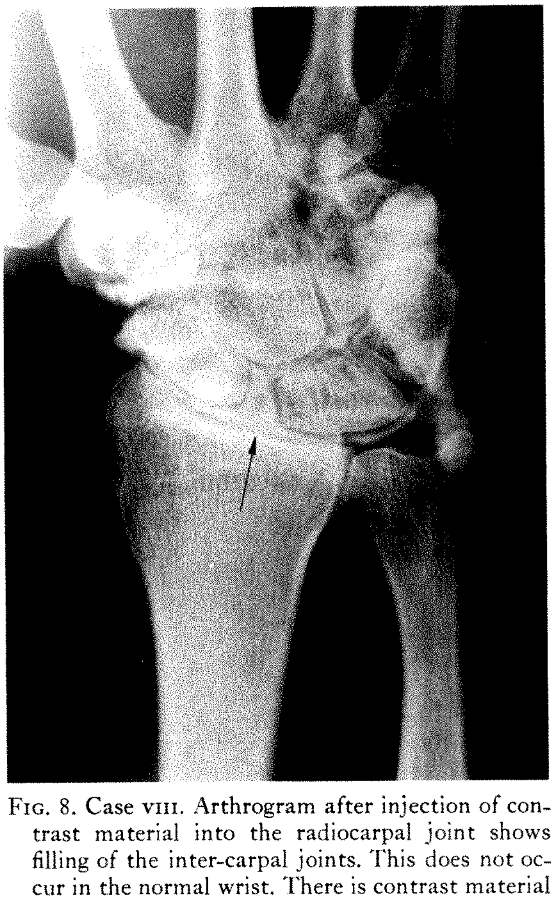

Fig. 8. Case viii. Arthrogram after injection of contrast material into the radiocarpal joint shows filling of the inter-carpal joints. This does not occur in the normal wrist. There is contrast material in the navicular-lunate gap (arrow).

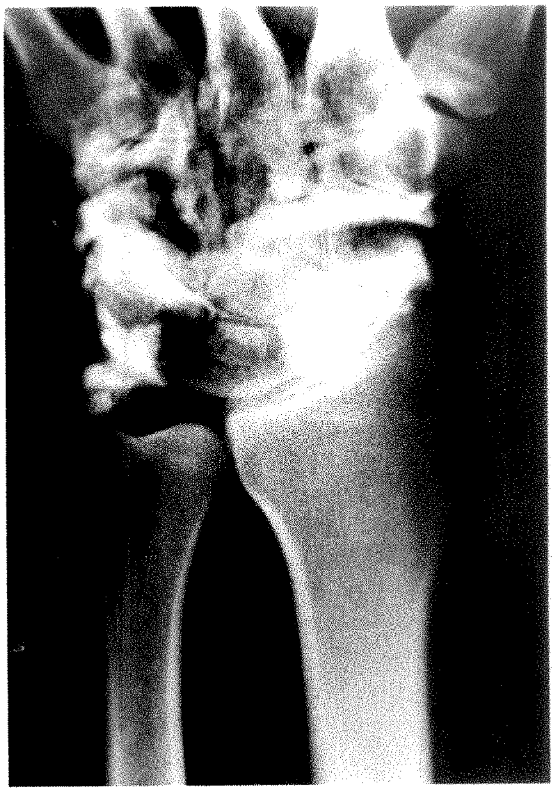

Fig. 9. Case iv. Arthrogram shows abnormal filling of inter-carpal joints. Navicular-lunate gap contains contrast material but it is partially obscured by overlying synovial recess.

Additional evidence that radial deviation usually accentuates the subluxation was found. Seven abnormal wrists had views in radial deviation and in neutral position or ulnar deviation, and in six of these, radial deviation caused a greater navicular-lunate gap and more obvious navicular foreshortening. In one wrist, there was greater foreshortening but the gap was smaller in radial deviation. Two wrists showed more

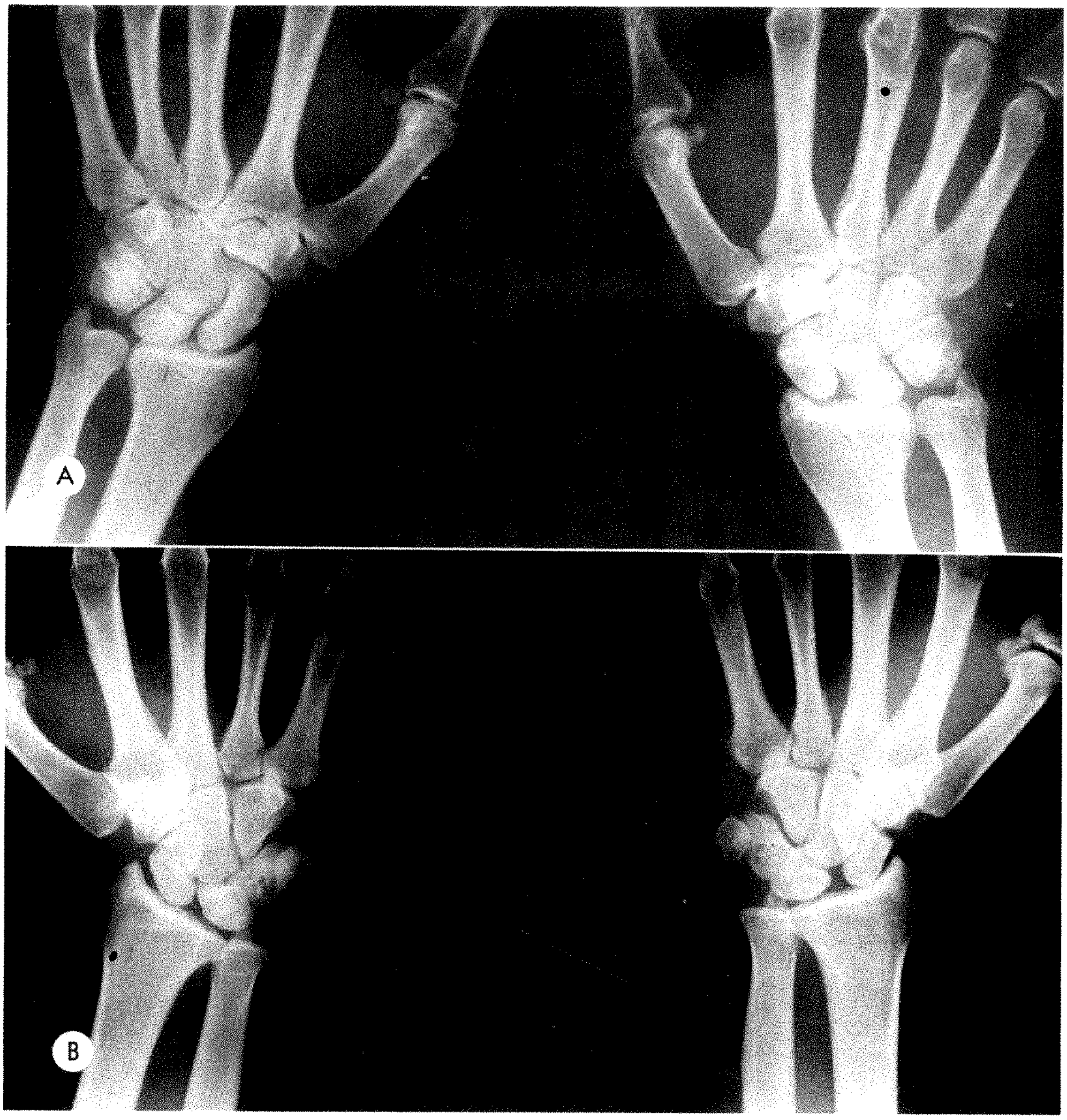

Fig. 10. Case xiv. (*A*) In pronation, there is foreshortening of the right navicular with a ring sign. Small navicular-lunate gaps are seen in both wrists. (*B*) In supination, the abnormal signs of rotatory navicular subluxation are accentuated. Notice that the hands are in greater radial deviation than they were in pronation.

distinct abnormalities in neutral position than in ulnar deviation. A ring sign may be seen in the normal wrist on a roentgenogram taken with the hand in marked radial deviation. This was found in the normal wrist of one patient in this series but there was no accompanying navicular-lunate gap, and other views were normal.

In addition to radial deviation, the other important aspect of positioning is obtaining a proper posteroanterior projection. A lack of overlap of radius and ulna at their distal articulation was considered to represent the ideal projection. Increasing overlap indicated a greater degree of obliquity. In three wrists, proper posteroanterior roentgenograms demonstrated the rotatory subluxation better than films made in very slight obliquity (Fig. 11). In one wrist, a roentgenogram made with the hand in neutral position showed a more distinct abnormality than one with the hand in radial deviation, and in this case the neutral film was a better posteroanterior projection. In two wrists it was very difficult to detect the abnormal signs and in both roentgenograms the wrists were in a slightly oblique projection. Finally, in four of the five supination views which failed to improve visualization of the abnormality, the supination view was slightly more oblique when compared with the pronation view. Therefore, a proper posteroanterior projection with no overlap of radius and ulna allows better visualization of the abnormal navicular position, especially the navicular-lunate gap.

The values of the measured radio-navicular angle varied widely for several reasons. It is often difficult to draw an accurate line representing the long axis of the navicular. No definite points define this line, and the outline of the bone is not easily seen on many routine lateral roentgenograms. Also, the extent of superimposition of the radius and ulna varies a great deal due to varying degrees of pronation and supination and slight tilting of the wrist from a precise lateral position. These differences will change the radio-navicular angle projected onto the film. Crittenden *et al.*[5] used tomography to clearly outline the navicular, but this technique alone does not control the variables of positioning. The measured radio-navicular angles in wrists with rotatory subluxation in this series, which averaged one hundred and twenty-seven degrees, were higher than those of Crittenden and his associates'[5] patient which were one hundred and fifteen degrees and one hundred and sixteen degrees. The range of values in the present series was very wide and there was considerable variation in the same patient between examinations. The angles in normal wrists were larger, averaging one hundred and fifty degrees, but they also displayed a wide range of values and variations between examinations. Good lateral roentgenograms without dorsal or

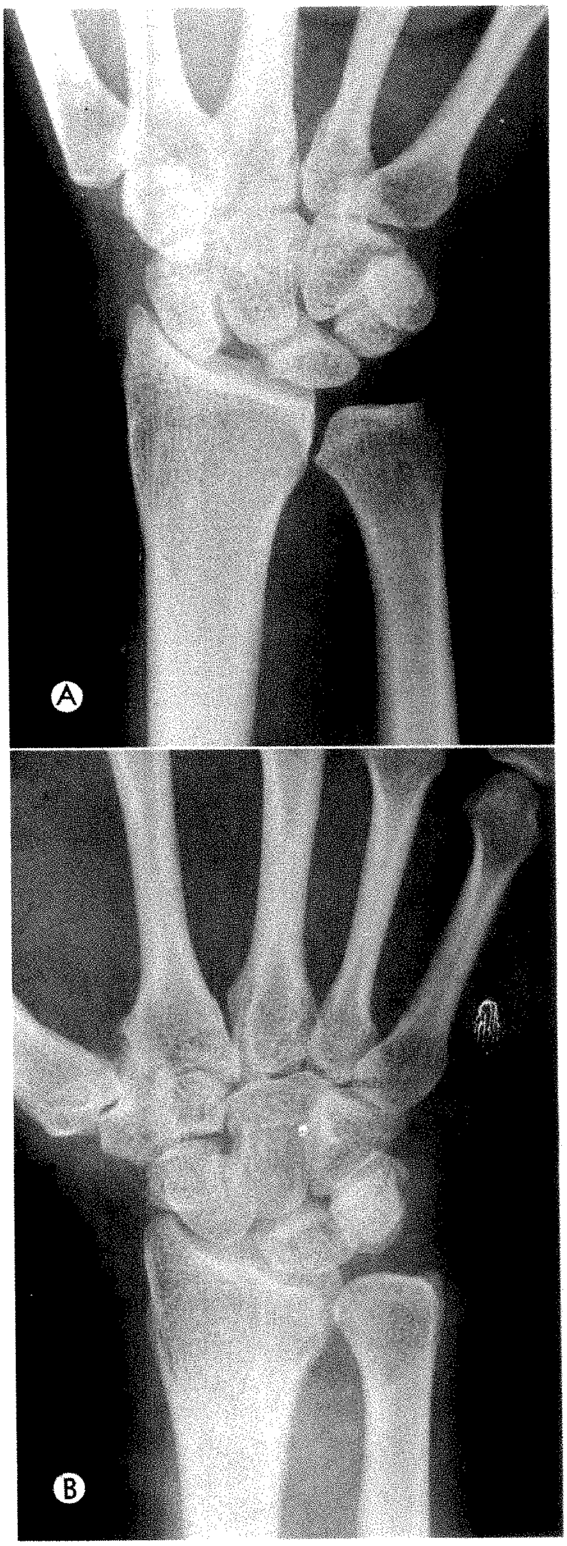

Fig. 11. Case xii. (*A*) A good posteroanterior view shows navicular-lunate gap. (*B*) Slight obliquity of the wrist (radius and ulna slightly overlapped) obscures the gap.

volar flexion of the hand will demonstrate the abnormal position of the navicular. However, clinical roentgenograms are seldom so consistently positioned, making the measurement of a radio-navicular angle on the lateral roentgenogram unreliable. Moreover, the signs on the properly positioned frontal roentgenogram are so diagnostic that this measurement is unnecessary.

Wrist arthrography may be helpful to confirm the diagnosis. In the normal wrist arthrogram, contrast material injected into the radiocarpal joint does not enter the inter-carpal joints.[7,10] In the two wrist arthrograms in this series, filling of both the inter-carpal and radiocarpal joints indicated disruption of inter-carpal ligaments.

The precise mechanism of injury that results in rotatory subluxation of the carpal navicular is poorly understood. It appears that the ligamentous attachments of the distal pole of the navicular are intact, but the proximal navicular-lunate ligament and the dorsal capsule of the wrist joint are disrupted. This allows dorsal or posterior rotation of the proximal pole of the navicular.[2,3,8,13] Armstrong[2] severed the navicular-lunate ligament in an amputated specimen and found that the navicular rotated dorsally during palmar flexion. England[6] divided the dorsal ligament of the wrist as well as the navicular-lunate ligament in a cadaver and could then sublux the navicular. He restored stability in the specimen by reefing and repairing the dorsal capsule of the wrist. It is easy to understand how such extensive ligamentous damage could occur during the severe trauma of a perilunate dislocation, but it is difficult to decide exactly what has happened to the wrists of those patients who have had only minor injuries or no apparent trauma.

Although patients with rotatory subluxation of the carpal navicular may suffer pain and disability even without degenerative joint disease, the development of this complication may result in even more serious disability. The development of secondary degenerative changes in the wrist has not been sufficiently emphasized. Only three patients with rotatory subluxation of the navicular have been previously reported in whom there was a significant and presumably secondary degenerative joint disease of the wrist.[2,3,11] Crittenden *et al.*[5] and England[6] implied that the injury would, if left alone, lead to degenerative disease of the wrist, but their cases did not illustrate this complication. Eleven of the nineteen wrists in this series (fifty-eight percent) had degenerative joint disease of the wrist, emphasizing the importance of this complication. The development of degenerative joint disease was documented in several cases as illustrated in Case v (Fig. 6, *A* and *B*). In view of this association, wrist roentgenograms showing degenerative joint disease of the radiocarpal joint should be examined carefully for the presence of a rotatory subluxation.

A detailed discussion of the treatment of rotatory subluxation of the navicular is beyond the scope of this paper. Patients with mild symptoms may require no treatment or only restriction of activities. Open reduction and repair of soft tissues are probably most useful when the subluxation has occurred recently. More extensive surgery, such as proximal carpal row resection, may be required when severe symptoms and advanced degenerative changes are present. It is not yet clear whether all patients with rotatory subluxation of the navicular will develop significant disability, but many will do so.[12,13] In any event, rotatory subluxation of the carpal navicular should be diagnosed and the patient referred to the care of an orthopedic surgeon familiar with the entity in order to minimize disability by preventing deterioration of wrist function.

SUMMARY

Rotatory subluxation of the carpal navicular, resulting from disruption of the navicular-lunate ligament, is a well recognized complication of lunate or perilunate carpal dislocation and of rheumatoid arthritis. It also occurs as an isolated abnormality in patients with vague or remote

histories of trauma, and in these patients the correct diagnosis is often not immediately made.

Clinical records and roentgenograms of sixteen patients with nineteen wrists involved by isolated rotatory navicular subluxation were reviewed. A navicular-lunate gap was present on the roentgenograms of all nineteen wrists. Foreshortening of the long axis of the navicular was evident in seventeen wrists, and all but one of these showed a navicular ring sign. These abnormalities are best demonstrated on roentgenograms centered over the wrists with the hand in slight radial deviation. There must be precise posteroanterior positioning since slight obliquity may obscure the gap. Lateral roentgenograms showed an abnormal position of the navicular in only six wrists, and measurement of the radionavicular angle was unreliable. Wrist arthrograms in two patients showed abnormal communication between radiocarpal and inter-carpal joints.

Several patients had only mild symptoms and were treated conservatively. Others required open reduction and soft tissue repair, or proximal row resection. All patients with rotatory subluxation may not have significant disability, but some certainly will. Degenerative joint disease was found in fifty-eight percent of the involved wrists. Progression of degenerative arthritic changes, primarily involving the radiocarpal joint, was documented in serial roentgenograms of several patients.

Rotatory subluxation of the carpal navicular should be included in the differential diagnosis of any patient with wrist pain.

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THE NOTCHED ARTICULAR PROCESS OF C7 (DORSALIZATION OF C7)*

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ABSTRACT:

The frequency of variation from the standard in the articular processes of C7 is very high (43.9 percent). These variations are:

(1) A notch on the back of the superior articular facet.

(2) Elongation of the "articular pillar" so that the posterior edge of the inferior articular process of C7 lies backward in relation to the posterior edges of the other cervical articular process.

(3) A combination of both.

Item 1 should not be mistaken for a fracture and item 2 should not be mistaken for a dislocation. These variants represent a partial dorsalization of C7.

THE upper and lower articular processes of a cervical vertebra are fused together forming the articular pillar. In the lateral cervical spine film, the articular pillar has the shape of a rhomboid. In some cases, the superior articular facet of C7 (Fig. 1), and less commonly C6, appears notched. This has been considered a normal variation.[3-5] On the other hand, it has been mentioned as a possible sequela of trauma.[7] This notch is not mentioned in the standard textbooks of anatomy studied in medical schools.[1,2] We noticed this finding frequently in patients who came for cervical spine studies for causes other than trauma, and who deny a history of trauma to the cervical spine. Still, the possibility that this might be the result of unrecognized minor trauma is raised. Therefore, we tried to determine the frequency of this finding and its relationship to age.

MATERIAL AND METHOD

Unselected normal lateral views of the cervical spine from the collection at the Children's Hospital were studied. The children were asymptomatic and had no history of trauma. If the articular process of the lower cervical spine could not be visualized adequately for evaluation, the case was rejected. Cases were divided only according to age. Seventy-two cases were reviewed in this manner. The ages of the children ranged between four months and twelve years.

We looked for: (1) a notch on the pos-

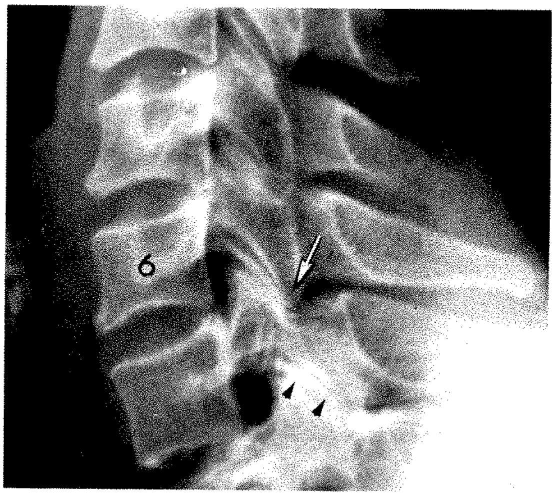

FIG. 1. Adult patient with no history of trauma. There is a large notch on the back of the articular process of C7. The white arrow points to the notch which corresponds to the most posterior part of the superior articular facet. Note that the inferior articular facet of C7 lies more posteriorly (arrowheads) than the superior articular facet. The region of the notch, in fact, represents the narrowing corresponding to pars interarticulare of a lower vertebra. Note that the articular element of C7 has lost its rhomboid shape (compare with C6).

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terior surface of the superior articular process (Fig. 2) (small or prominent notch); (2) elongation of the articular pillar, so that the inferior articular facet does not lie directly below the superior, and, therefore, the "articular pillar" is not rhomboid in shape. In these instances the inferior articular facet lies in a more posterior position than that usually seen in the typical cervical vertebra, and is therefore no more an articular pillar (Fig. 3); and (3) constriction at the junction between the superior and inferior articular process (Fig. 4). This is in fact a combination of (1) and (2), but it is classified here as a separate item for convenience. Six children were below two years of age, and in all of them the articular process was not developed enough to be roentgenologically adequate for this study. The number is thus reduced to 66 children, ages two to twelve years.

RESULTS

In the 66 children evaluated (Table 1), we found that 37 cases (56.1 percent) were "negative." That is, the articular processes of the lower cervical vertebra (C6 and C7) were rhomboid in shape as in the typical cervical vertebrae. In 29 cases (43.9 percent), the articular processes of C7 showed variation from the typical cervical vertebral standard. Of these 29 cases with a variant, seven cases (10.6 percent), ages three to ten years, showed a notch on the upper articular facet (three small and four prominent). Elongation of the articular pillar so that it loses its rhomboid shape was seen in 22 cases (33.3 percent), ages three to twelve years. Of these 22 cases, constriction at the junction between the superior and inferior articular processes was seen in 14 cases (21.2 percent), ages four to twelve years. In eleven of them, the superior and inferior articular processes ap-

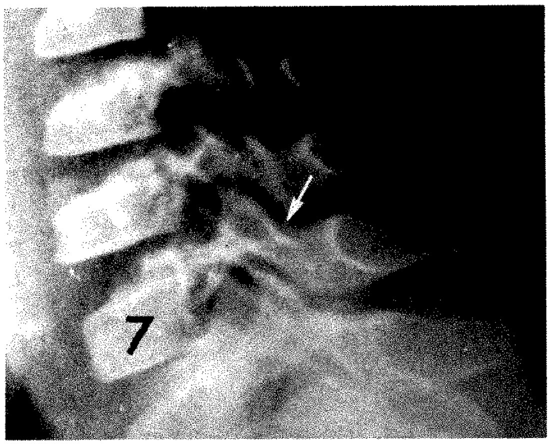

Fig. 2. Seven year old child. A notch is noted on the back of the articular process of C7 (arrow).

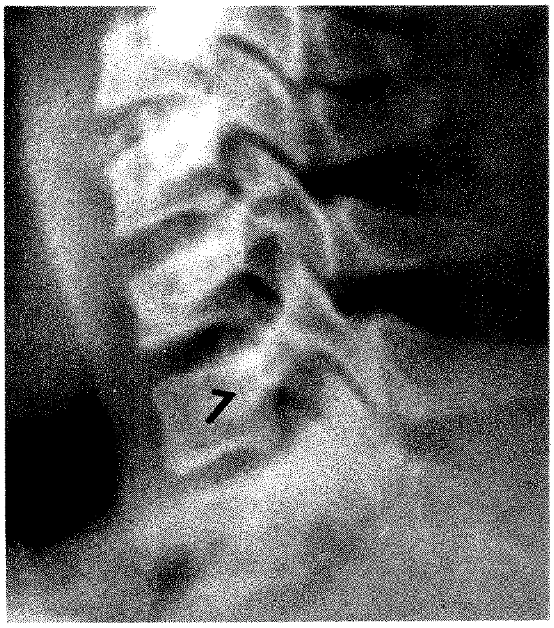

Fig. 3. Eleven year old child. The articular "pillar" of C7 is elongated, and the inferior articular facet of C7 lies more posteriorly than the upper one.

Table I

	Number of Cases	Percent of Total Cases
Total cases	66	100
"Negative"	37	56.1
Notch on superior articular facet of C7	7	10.6
Elongated articular pillar of C7 without a notch	8	12.1
Elongated articular pillar of C7 with tiny notch	3	4.5
Elongated and notched articular process of C7	11	16.7

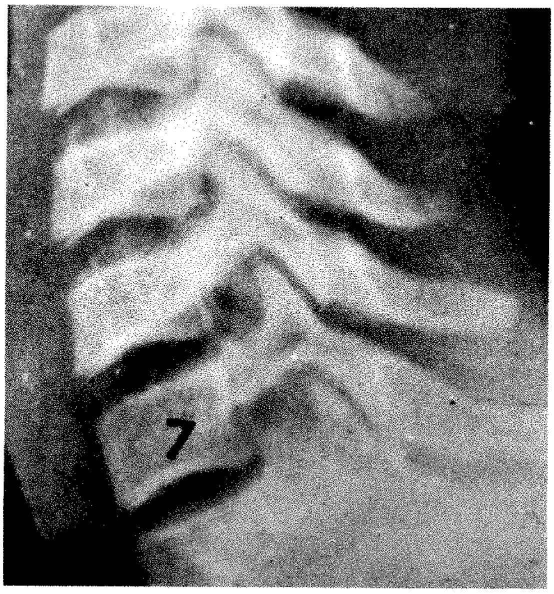

Fig. 4. Twelve year old child. There is elongation of the articular element of C7. The inferior articular process is posteriorly placed in relation to the superior articular process. There is slight constriction between the superior and inferior articular process, giving the semblance of pars interarticulare.

peared as if they were separated by a distinct pars interarticularis similar to the condition seen in the upper thoracic spine.

In two of the "positive" cases, we found a notch on the superior articular facet of C6, in addition to the changes seen in C7.

DISCUSSION

A transitional vertebra is not an unusual observation at the junctions of cervicothoracic, thoracolumbar, and lumbosacral regions. The vertebral arches are the ones usually affected by these variations. The most common variation seen at the cervicothoracic region is that which gives C7 an appearance similar to an upper thoracic vertebra.[6] According to Gorlitz, as quoted in Schmorl and Junghans,[6] about 45.9 percent of all cervical spines show this variant which could be considered dorsalization of C7. The common variants mentioned are the broadened and elongated transverse process of C7 and cervical ribs. No mention is made of changes in the articular facets. We endeavored to look at the variants in the articular process of C7 and were impressed by the frequency with which we encountered these variations (43.9 percent).

Elongation of the articular component, so that the inferior articular process lies farther posterior than the superior articular process, was seen in 33.3 percent of the normal children. With this change in shape, the articular pillar, in fact, ceased to exist. A line drawn through the posterior edge of the articular facets of the cervical spine would in this case pass through the posterior edge of the superior articular process, but would be anterior to the inferior articular facet of C7. Thus, the posterior edge of the articular component lies behind the line that connects the posterior edges of the articular process of the rest of the cervical spine. Mistaking this finding for backward dislocation of C7 could be a source of error, especially when the body of C7 is underexposed and its alignment cannot be properly seen. In the occasional cases when this variation is seen in C6, the same mistake may be committed.

Table II

Age Years	Negative	Elongated C7 Articular "Pillar" without or with Tiny Notch	Notched Articular Process	"Pars Interarticulare"	Total
2	1	0	0	0	1
3	5	1	2	0	8
4	4	3	0	1	8
5	9	2	0	4	15
6	4	0	0	0	4
7	1	0	1	3	5
8	5	1	1	0	7
9	3	0	0	1	4
10	3	2	3	0	8
11	1	1	0	0	2
12	0	1	0	2	3
13	1	0	0	0	1
Total	37	11	7	11	66

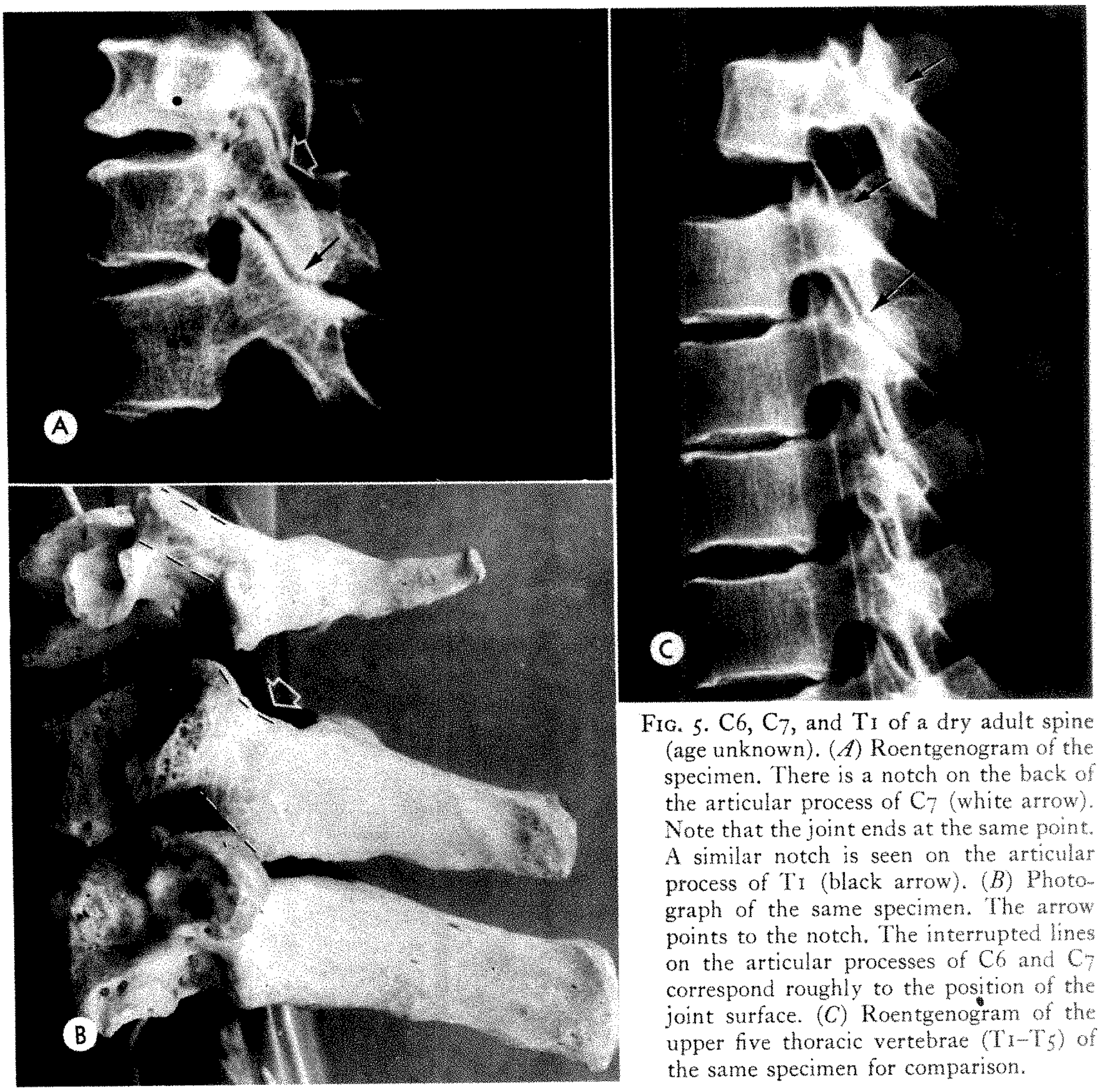

Fig. 5. C6, C7, and T1 of a dry adult spine (age unknown). (*A*) Roentgenogram of the specimen. There is a notch on the back of the articular process of C7 (white arrow). Note that the joint ends at the same point. A similar notch is seen on the articular process of T1 (black arrow). (*B*) Photograph of the same specimen. The arrow points to the notch. The interrupted lines on the articular processes of C6 and C7 correspond roughly to the position of the joint surface. (*C*) Roentgenogram of the upper five thoracic vertebrae (T1–T5) of the same specimen for comparison.

A notch at the "back" of the superior articular process of C7, and much less commonly of C6, is occasionally mistaken for a fracture. We do not think that such a high percentage of small children would already have had trauma of the cervical spine (see Table I). Two out of eight patients at the age of three showed this notch. This percentage did not increase with age, as would have happened had this been a sequela of an accident (Table II).

Combination of the above mentioned findings, that is, elongation of the articular process plus a notch and constriction behind the superior articular facet, brings the articular process into a form nearer to that of an upper thoracic vertebra than that of a cervical vertebra (Fig. 1). The constricted area between the superior and inferior articular processes is equal to pars interarticularis.

Three vertebrae (C6, C7, and T1) were separated from the rest of a dry spine and were both photographed and x-rayed. We found a notch on the articular process of C7 in the roentgenogram (Fig. 5*A*) which was difficult to show on many different photographs of the same specimen. Figure 5*B* shows the notch better than all the other photographs. This difficulty is probably the reason why the notch is not mentioned in the standard textbooks of anatomy.

We believe, therefore, that the above mentioned findings in C7 (and much less frequently and prominently in C6) are normal variants, and may be considered as partial dorsalization of C7.

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VOL. 126, No. 3

SPINAL NEUROFIBROMATOSIS*

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ABSTRACT:

Neurofibromatosis is a congenital abnormality due to maldevelopment of the neurectoderm and mesoderm. Spinal abnormalities are a frequent occurrence and the roentgenological changes observed in 21 patients are presented. These include scoliosis, posterior scalloping of vertebral bodies, and the roentgenological features associated with intraspinal tumors and thoracic meningoceles.

NEUROFIBROMATOSIS is a congenital process inherited as a mendelian dominant. The site of origin of this dysplasia is in the neurectoderm and mesoderm, therefore, the body parts involved are the skin, soft tissues, bones, and central nervous system. Diffuse systemic or regional involvement frequently exists while occasionally a forme fruste may be encountered with only one of the manifestations present.

This presentation will be limited to a discussion of spinal neurofibromatosis. Spinal involvement is reflected in a multitude of changes involving the osseous structures, paraspinal tissues, and the intraspinal contents. This involvement of multiple areas results in diverse presentations which include: scoliosis, paraspinal neurofibromas, extradural and intradural neurofibromas, congenital intramedullary tumors, syringomyelia, the scalloping of single or multiple vertebral bodies, and dural ectasia and thoracic meningocele. Examples of the protean manifestations of spinal neurofibromatosis will be presented.

SCOLIOSIS

Scoliosis is a frequent occurrence in patients with neurofibromatosis and has been reported to occur in approximately ten percent of cases.[3,5] The degree of curvature is variable, although most authors consider the sharp angle curve as being characteristic.[2,3,6]

The reasons for the development of the scoliosis in this group of patients as suggested by Hunt and Pugh[3] and Mezaros *et al.*[6] are:

1. Mesenchymal defect (bony spinal canal forms in mesoderm).
2. Thoracic meningocele (bone erosion).
3. Intraspinal or paraspinal tumors, or both.

The mesenchymal defect may result in maldevelopment of one or more vertebral

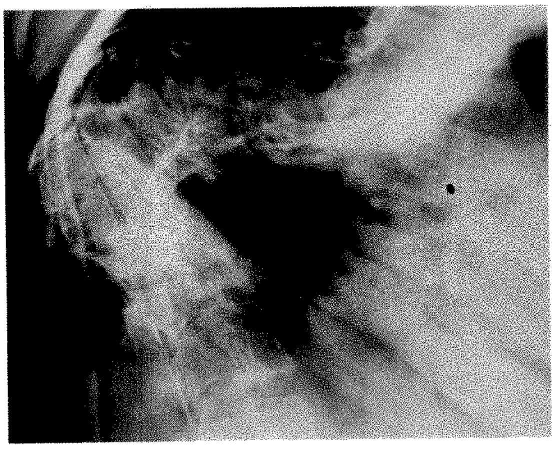

FIG. 1. Scoliosis in 45 year old female with stigmata of neurofibromatosis. Sharp angle curve to the right is present. Ribbon ribs are noted. The cause of the change in this instance is a dumbbell neurofibroma with a paraspinal and intraspinal component.

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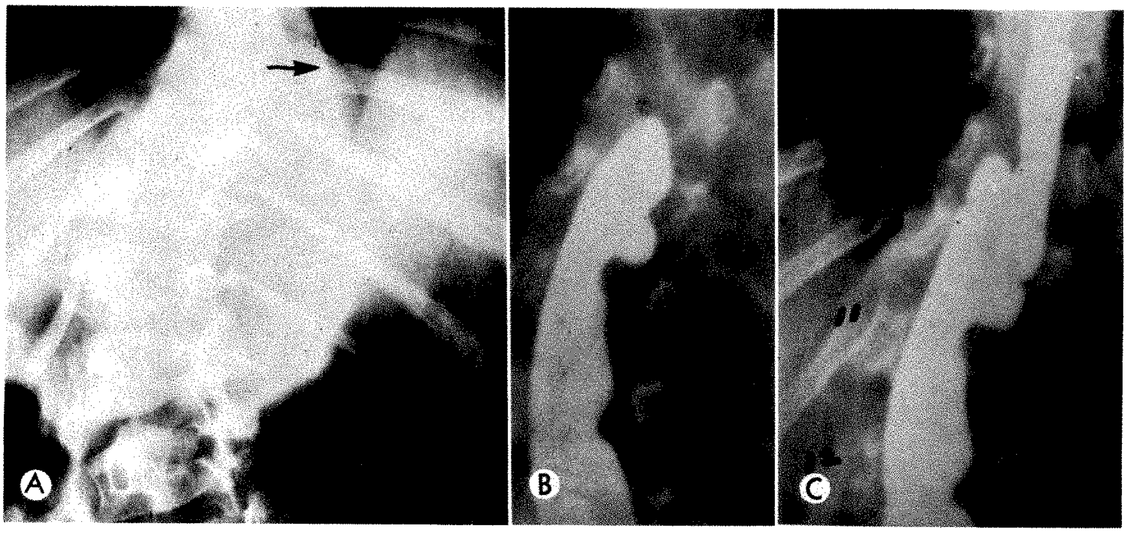

Fig. 2. Scoliosis in child with dumbbell neurofibroma. Mild thoracolumbar scoliosis in eight year old male with no overt sign of neurofibromatosis. (*A*) A paraspinal mass is observed in the left paravertebral gutter (arrow). (*B* and *C*) An epidural component is identified on the left at myelography (arrows).

bodies which may account for an abnormal curvature of the spine.

Thoracic meningoceles are a consequence of malformation of the meninges and the bony spinal canal. The constant pulsations of a meningocele will produce bone erosion and thus may lead to scoliosis.

Finally, the occurrence of paraspinal or intraspinal tumors may result in curvature of the spine as a result of bone erosion and may even produce weakness of muscle groups with resultant overactivity of uninvolved muscles.

In addition to the S shaped curvature, attenuation of posterior ribs may result in a "twisted ribbon" appearance.[3]

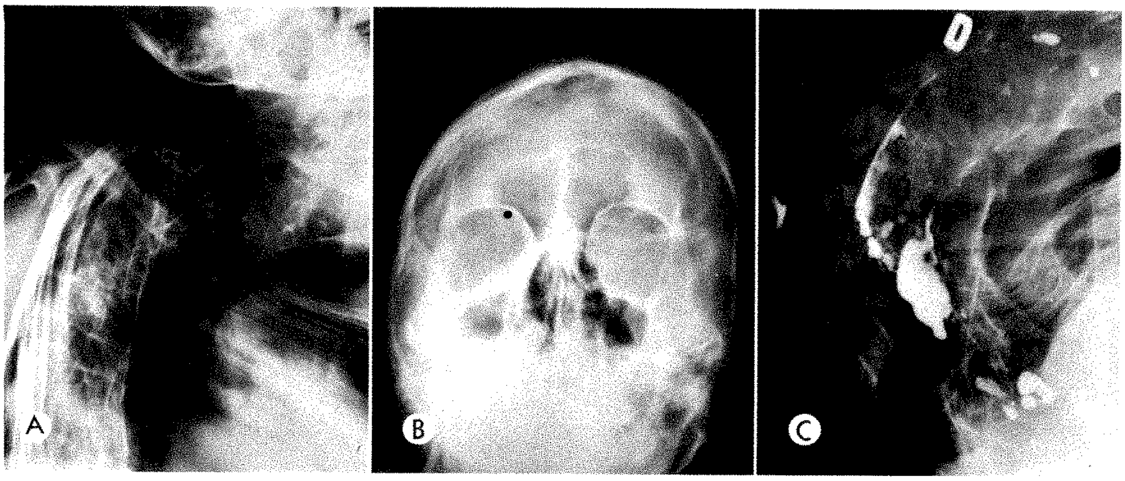

Fig. 3. Adult male with neurofibromatosis, scoliosis and intraspinal epidermoid tumor. (*A*) Sharp angle scoliosis with ribbon ribs. (*B*) Partial absence of sphenoid bone on right. (*C*) Complete obstruction to pantopaque column in thoracic region. The "D" on the roentgenogram marks the site of obstruction noted when pantopaque was instilled from above. Pantopaque injected from below (arrow) is stretched out against pedicles on right. These findings indicate an intramedullary lesion, either a tumor or torsion of the cord due to the scoliosis with secondary cord swelling. At surgery an intramedullary, epidermoid tumor was removed.

In the present series of 21 patients with evidence of spinal neurofibromatosis, three demonstrated severe scoliosis. Two patients had sharp angled curves while one was moderate.

A 45 year old woman presented with a severe S shaped scoliosis and "ribbon" ribs. In addition to the attenuation of the ribs, erosion of several ribs was observed as a consequence of a dumbbell neurofibroma which was both paraspinal and intraspinal (Fig. 1).

An eight year old boy was observed for evaluation of scoliosis, and a paraspinal mass with rib erosion was also found. At myelography a dumbbell neurofibroma was demonstrated producing the extradural mass (Fig. 2, *A* and *B*).

In the third case, a patient with sharp angled scoliosis presented with severe respiratory distress and progressive paraparesis (Fig. 3, *A–C*). This patient had no overt stigmata of neurofibromatosis; however, skull roentgenograms revealed an absence of part of the sphenoid bone on the right (Fig. 3*B*) which is a characteristic finding in neurofibromatosis. A complete block (Fig. 3*C*) was demonstrated at myelography. The pantopaque column at the margin of the block was elongated and displaced laterally by an intramedullary mass. A problem arose as whether these changes were due to tethering of the cord with swelling due to the severe scoliosis or to an intramedullary tumor. At surgery an intramedullary epidermoid tumor was present.

OCCURRENCE OF OTHER TUMORS

An increased incidence of tumors other than neurofibromas occurring within the central nervous system in patients with the phakomatoses has been observed. In this series two patients had other tumors in the central nervous system. One patient had an epidermoid in the thoracic region (Fig. 3). The second patient was an eight year old girl with typical stigmata of neurofibromatosis who had neurologic signs suggesting a mass in the cervical region. An expanding intramedullary lesion causing obstruction to the flow of pantopaque was identified in the cervical area (Fig. 4) on myelography. At surgery the lesion proved to be a syrinx with a dilated cystic cavity. This child has now been followed for seven years with no recurrence of symptoms.

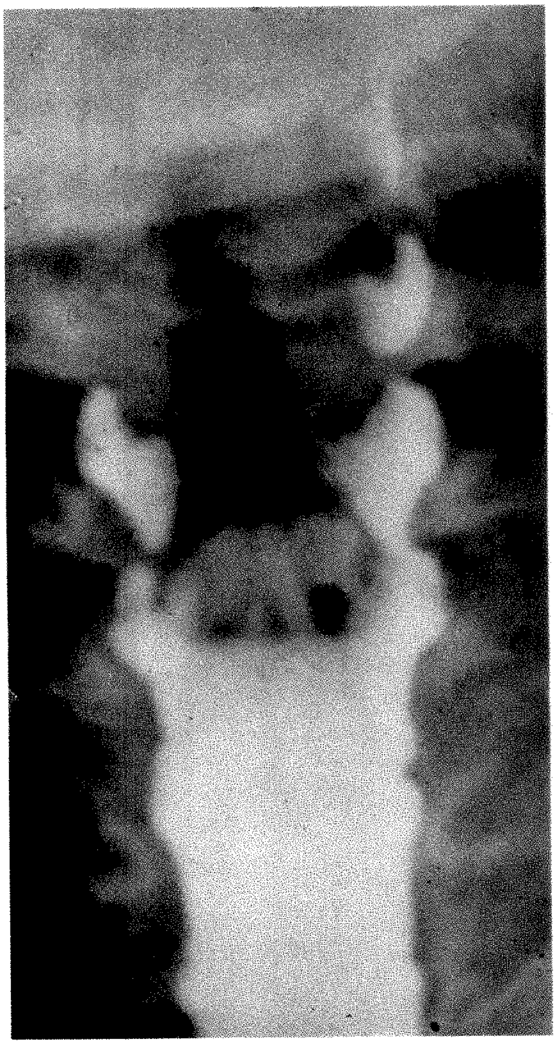

FIG. 4. Child with stigmata of neurofibromatosis and syringomyelia. An expanding, intramedullary lesion in the cervical region has produced a complete block. At surgery syringomyelia with cyst was present.

In this series of 21 patients, five (twelve percent) had intraspinal neurofibromas. Only one of these patients showed multiple lesions, while two had dumbbell neurofibromas.

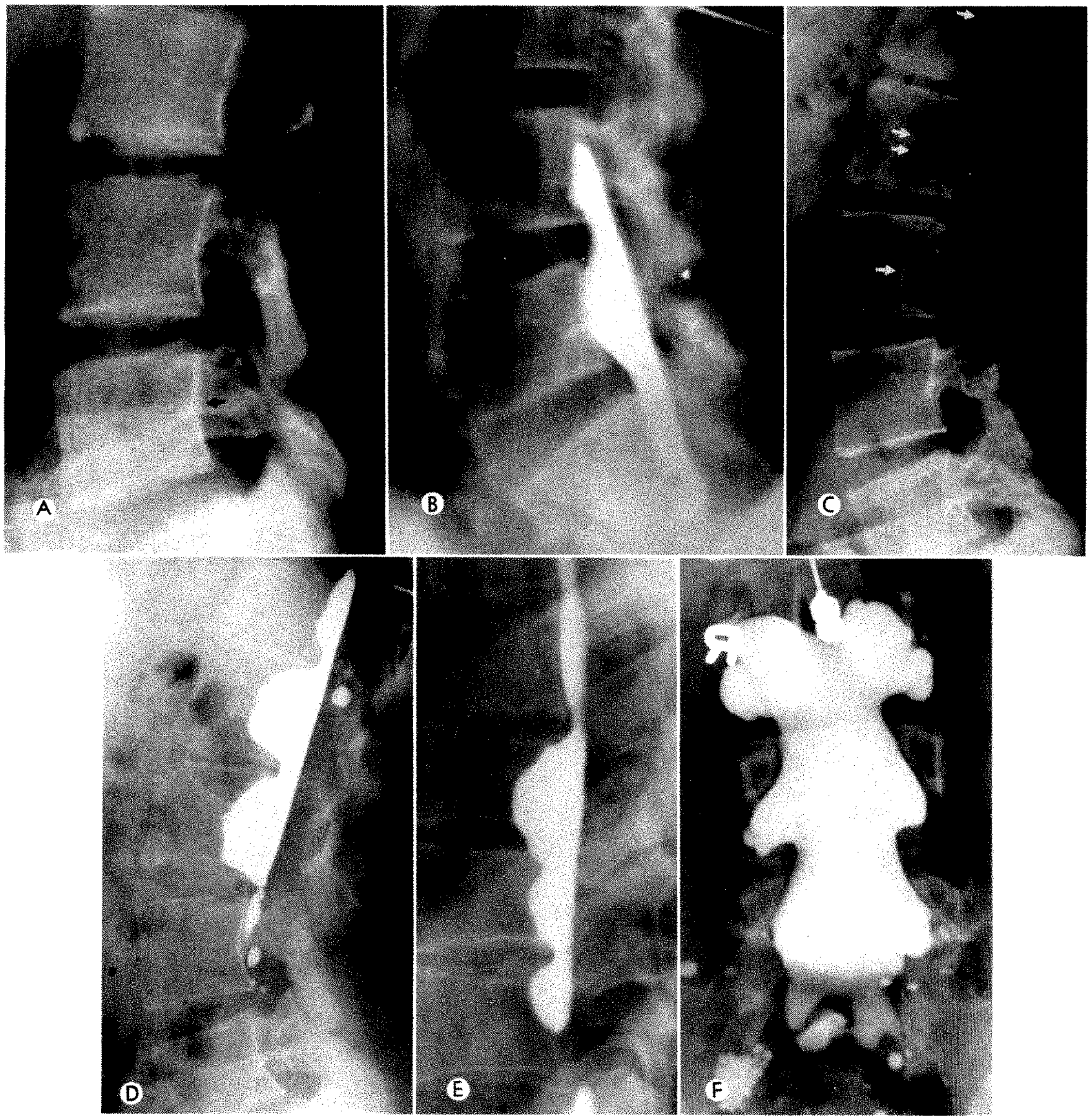

FIG. 5. Patient with neurofibromatosis demonstrating progressive scalloping of lumbar bodies. (*A*) Slight scalloping (arrows) of posterior surfaces of lumbar vertebral bodies. Interpediculate widening is not present. (*B*) The cause of the scalloping is dural ectasia demonstrated during lumbar myelography. (*C*) Four years later progression of scalloping is noted (arrows). At myelography, dural ectasia in the (*D*) lumbar and (*E*) thoracic regions is identified. (*F*) Enlargement of the subarachnoid space in the anteroposterior projection due to dural ectasia is now present with interpediculate widening.

VERTEBRAL BODY SCALLOPING

The scalloping of vertebral bodies may occur in a variety of disorders which affect the spine or its contents.[4,7,8] The most common cause of scalloping, with involvement of either single or multiple vertebral bodies, is neurofibromatosis. The scalloping occurs earlier than interpediculate widening because the spongy bone of the vertebral body offers less resistance to the pressure of the expanding intraspinal contents than does the compact bone of the pedicles. The most frequent cause of the scalloping in patients with neurofibromatosis is dural ec-

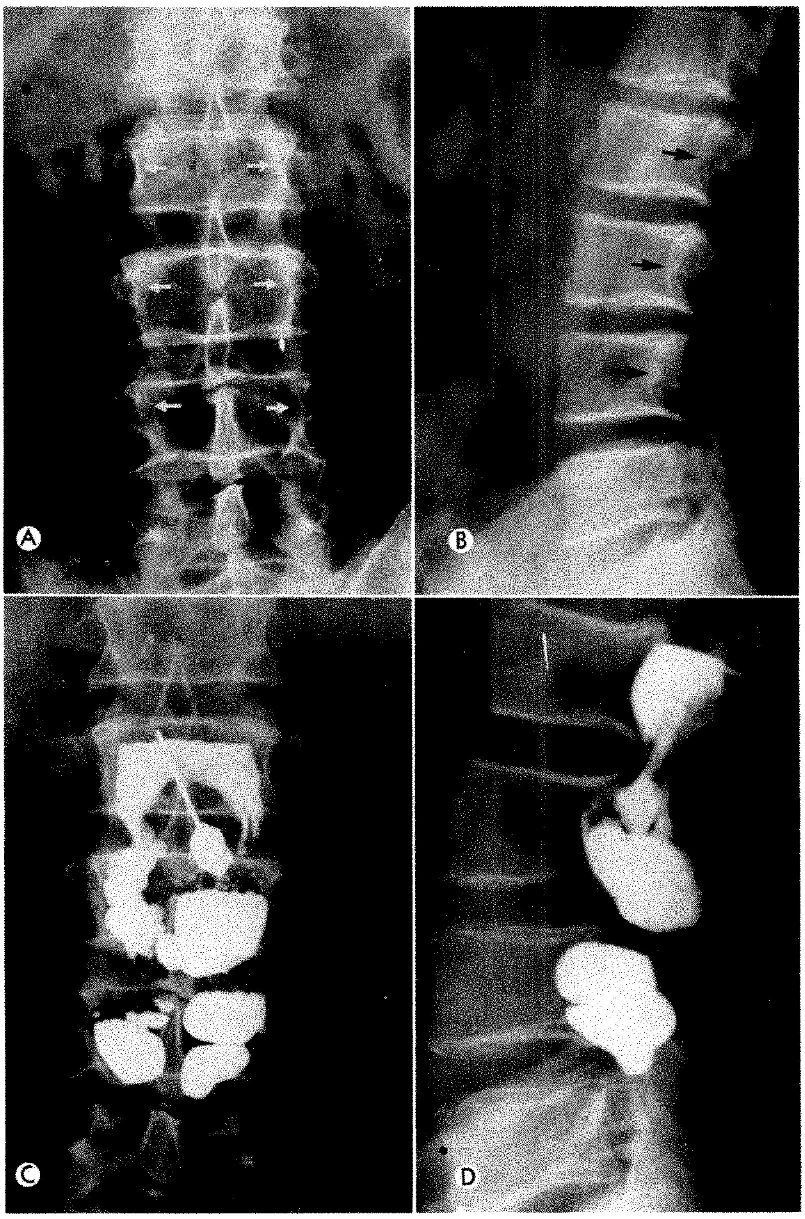

Fig. 6. Patient with neurofibromatosis with scalloping due to dural ectasia and large solitary neurofibroma. (*A* and *B*) Interpediculate widening and scalloping (arrows) of multiple lumbar vertebral bodies. (*C* and *D*) Dural ectasia with expansion of subarachnoid space is present in anteroposterior and lateral projections. A large solitary neurofibroma is also identified.

tasia. This ectasia is a consequence of dilatation of the subarachnoid space presumably as a result of the mesenchymal abnormality, frequently resulting in scalloping of the single or multiple vertebral bodies. Scalloping may be progressive, as demonstrated in a patient who presented with numbness of the lower extremities at the age 16 years. Mild scalloping was present with no interpediculate widening in the lumbar spine (Fig. 5*A*). A dilated subarachnoid space was observed due to dural ectasia (Fig. 5*B*). Four years later the patient was re-examined and showed marked

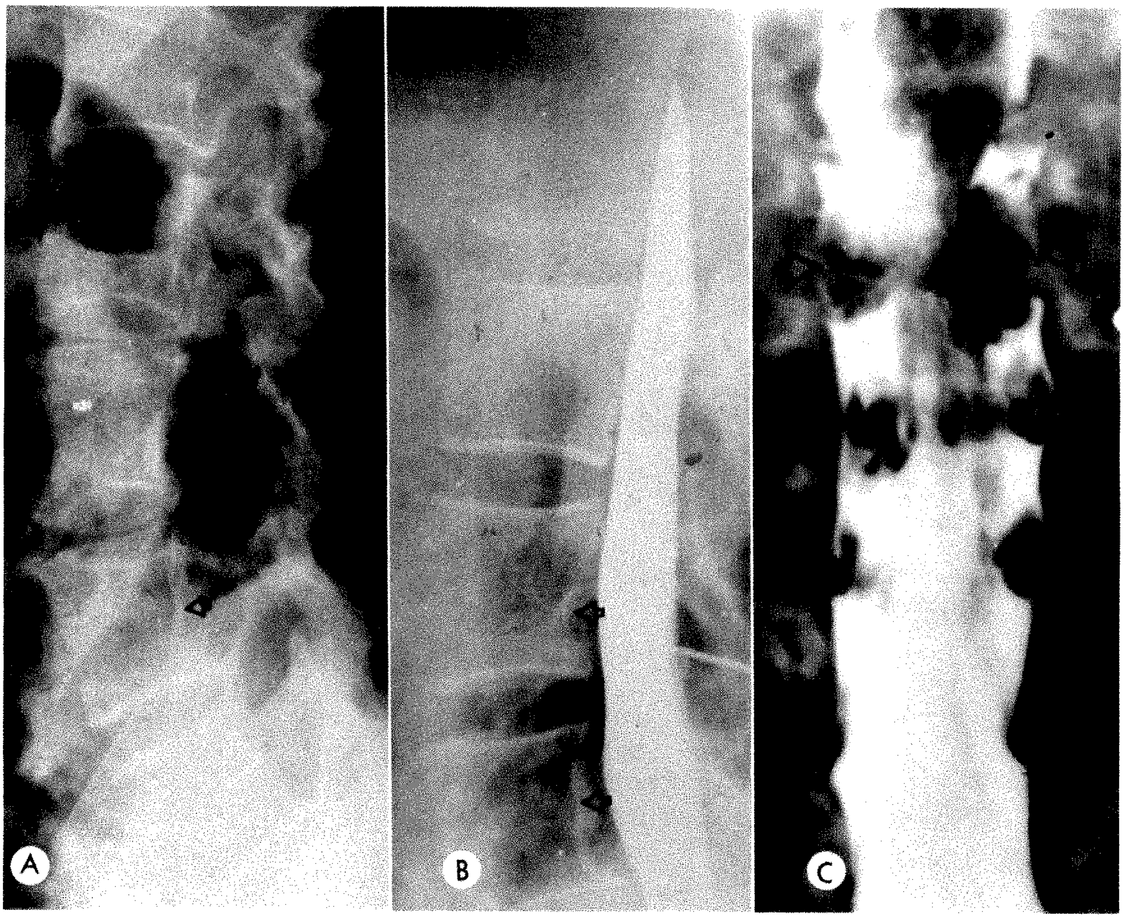

FIG. 7. Patient with stigmata of neurofibromatosis shows scalloping due to lumbar epidural neurofibromas and multiple nerve root neurofibromas. (*A*) Marked scalloping is present at several levels (arrows). (*B*) Lateral lumbar myelogram demonstrates scalloping due to epidural neurofibromas (arrows). No dural ectasia is present in this instance. (*C*) Anteroposterior projection of this cervical myelogram demonstrates multiple nerve root neurofibromas (arrows).

progression in scalloping with interpediculate widening in the thoracic and lumbar region. Dural ectasia was demonstrated on myelographic examination (Fig. 5, *C–F*). No tumor was encountered.

Another patient was observed with marked posterior scalloping and widening of the interpediculate distance in the lumbar region (Fig. 6, *A* and *B*). At myelography, a dilated subarachnoid space contributed to the scalloping, but in addition, a large solitary neurofibroma was demonstrated which also played a role in the roentgenological changes (Fig. 6, *C* and *D*).

A third patient with progressive neurologic disability and the stigmata of neurofibromatosis was studied. On the plain roentgenograms of the spine, scalloping and interpediculate widening were present (Fig. 7*A*). At myelography, however, no dural ectasia was observed; the vertebral body abnormalities in this instance were caused by multiple epidural neurofibromas in the lumbar region (Fig. 7*B*). In addition, neurofibromas were demonstrated at multiple levels in the cervical area (Fig. 7*C*).

A patient was examined for trauma to the cervical spine, and posterior scalloping of the C2 and C3 vertebral bodies was noted. Following myelography these changes were observed to be secondary to localized dural ectasia.

A young adult had a routine chest examination, at which time scalloping and interpediculate widening in the thoracic region were demonstrated (Fig. 8, *A* and *B*). At myelography the localized scalloping was due to a thoracic meningocele. Seventy percent of patients with thoracic meningoceles have neurofibromatosis.[1,6] These meningoceles occur more commonly on the right side and are frequently asymptomatic.[1]

Thus, scalloping when observed in patients with neurofibromatosis may be due to a variety of causes, including dural ectasia, neurofibroma, and thoracic meningocele.

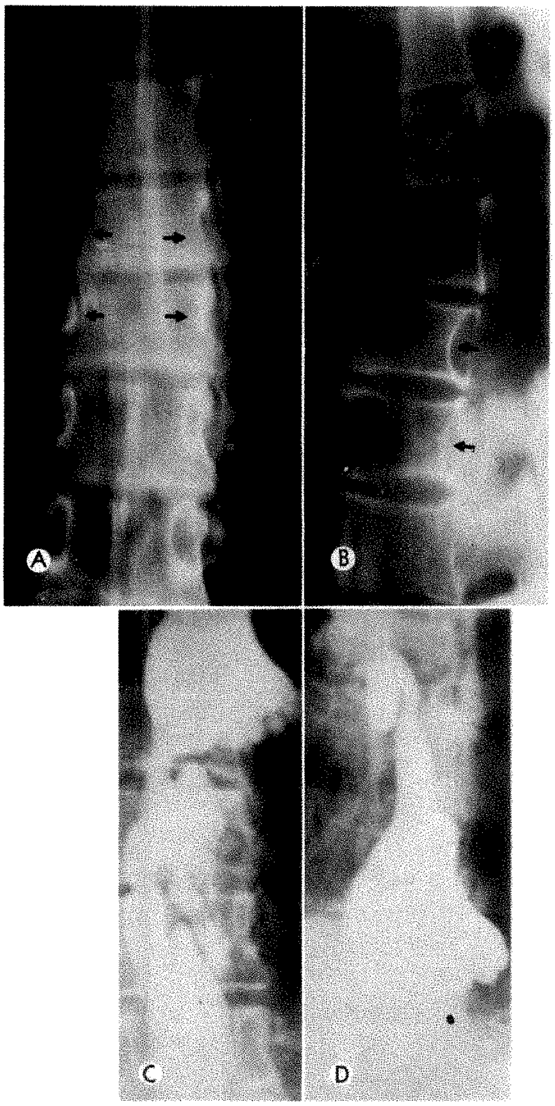

Fig. 8. Asymptomatic young adult male with thoracic meningocele and neurofibromatosis. (*A*) Anteroposterior and (*B*) lateral tomograms of thoracic spine demonstrate interpediculate widening and scalloping. (*C* and *D*) Anteroposterior thoracic myelogram illustrates expanded subarachnoid space with lateral meningocele on the left.

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MARCH, 1976

DEMONSTRATION AND DIMENSIONAL ANALYSIS OF THE NORMAL PANCREAS WITH GRAY-SCALE ECHOGRAPHY

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ABSTRACT:

For consistent identification of the normal pancreas, preliminary longitudinal scanning at, or near, the mid-line and subsequent oblique scanning in the long axis are necessary prerequisites in delineating the anatomic outline of the pancreas. The range of normal measurements for different anatomical regions of the pancreas was determined, based on the dimensional examinations of this organ in 328 patients free of pancreatic disease. These provide objective guidelines for analysis of the pancreas in abdominal echography. Echography provides a rapid, non-invasive method of imaging the pancreas. This study demonstrates that visualization of the pancreas as a separate structure does not imply that it is consequently abnormal.

THE pancreas is a difficult organ to examine by routine roentgenographic methods, radionuclide scanning, and angiography. In the recent literature there are few reports concerning the diagnostic value of pancreatic sonography.[1–9] However, virtually all of these reports indicate that the normal pancreas cannot be visualized; and that, indeed, if it is imaged, it is consequently abnormal.[1–6,8,9]

If the normal pancreas were demonstrable by sonographic means, this modality would become a more valuable diagnostic tool in the evaluation of potential pancreatic pathology. The purpose of this study is to demonstrate conclusively that the normal pancreas can be imaged routinely by echography.

MATERIAL AND METHOD

Conventional, commercially available, compound B-scan diagnostic ultrasound equipment with gray-scale capability was employed. The transducer was non-focused, operating at 2.25 MHz with a lead zirconate/titanate piezo-electric element.

All adult patients referred to the ultrasound laboratory for abdominal studies were prospectively scanned in the supine and prone positions with particular attention to the region of the pancreas.

The search for the pancreas was begun by longitudinal scanning at the midline or in the immediate parasagittal (longitudinal) plane on either side. This often resulted in displaying a separate, ovoid structure just anterior to the great vessels (Fig. 1). The cephalad and caudad boundaries of this structure (later proved to be the pancreas), for this one thin section, were outlined with wax marks on the patient's skin. Next, the transducer was moved laterally in 1 cm increments, both to the left and to the right of the midline. The parasagittal sections were repeated, and each time the cephalad and caudad margins of the pancreas were cutaneously marked. Thus, the entire outline of the pancreas was traced on the skin in two dimensions. This was followed by scanning in the transverse direction over this area, conforming to the marks on the patient's skin. If the pancreas lay in a horizontal plane, we could visualize the head, body, and tail in one transverse section. However, in the vast majority of cases, the pancreas was found to have an oblique, or even more complex, anatomic orientation within the abdomen. In such cases, we found that the oblique pancreatic scan following its long axis was most helpful (Fig. 2).

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A flexible wire superimposed on the sonographic boundaries of the pancreas on the skin (Fig. 3) was recorded on film (Fig. 4). Later, many of these same patients in our study underwent pancreatic duct cannulation and retrograde injection of contrast material (Fig. 5).

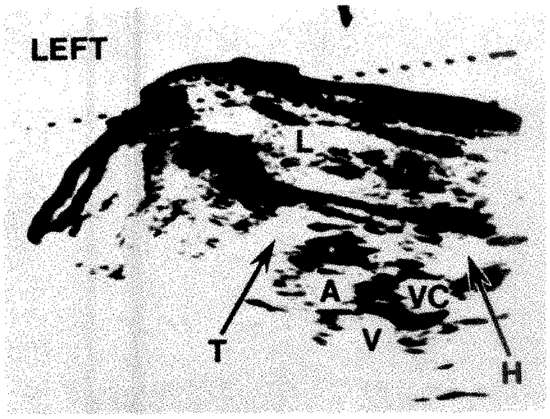

Fig. 2. Gray-scale display of normal pancreas. Supine oblique scan of upper abdomen in the long axis of the pancreas. The head (H) and body are well visualized. Only a portion of the tail (T) is demonstrated due to shadowing from overlying gas. The remainder of the tail is displayed on the prone scan (Figure 7). Normal echographic landmarks include: liver (L), vena cava (VC), vertebral column (V), and aorta (A).

RESULTS

Of the patients who underwent these prospective sonograms, 26 also had subsequent normal pancreatic ductograms and no evidence of pancreatic disease occurring within follow-up periods of four to 18 months. In 23 of 26 cases there was excellent correlation of pancreatic configuration and location as demonstrated by the two imaging modalities; the opacified ducts lay entirely within the outline shown by the wire.

Having thereby demonstrated that the normal pancreas indeed can be readily visualized by sonography, 382 normal subjects and patients with no evidence or suspicion of pancreatic disease were studied. These groups were randomly selected and were of varying body sizes. Sonographic measurements were obtained. The results are depicted in Table 1.

DISCUSSION

Our clinical experience previous to this study, and reports in the literature, indicated that the normal pancreas was only rarely imaged with ultrasonic B-scanning.

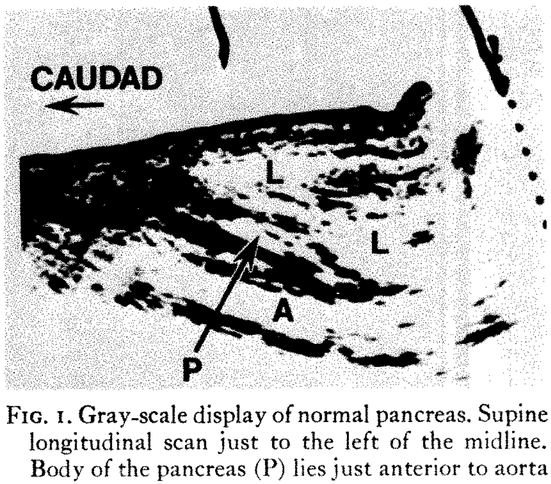

Fig. 1. Gray-scale display of normal pancreas. Supine longitudinal scan just to the left of the midline. Body of the pancreas (P) lies just anterior to aorta (A). Liver (L) serves as medium for good through transmission of ultrasonic beam.

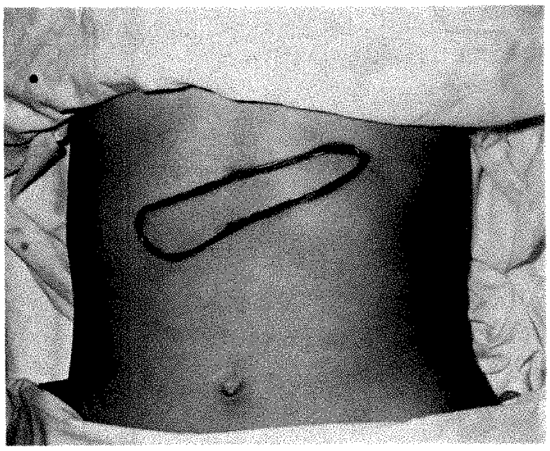

Fig. 3. Wire marking cutaneous projection of the sonographically determined pancreatic boundaries.

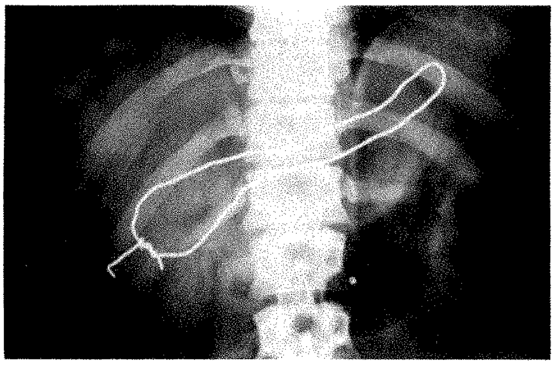

FIG. 4. Roentgenogram obtained with wire delineating margins of pancreas as determined by ultrasonic scanning.

There were three major reasons for this lack of visualization. The first was the highly variable size, shape, and location of the pancreas within the upper abdomen. Second, the normal pancreas produces multiple internal echoes, resulting in difficulty with its consistent delineation as a distinct organ against the background of the neighboring structures. This is in contradistinction to other abdominal organs such as the kidney, liver, and spleen. This discrepancy is most likely due to the relative histological inhomogeneity and fibrous nature of the pancreas.[3] Third, probably the most important cause of previous failure to visualize the normal pancreas, is in the area of instrumentation. The advent of gray-scale display has resulted in superior images of the abdomen. Prior to this advance in technology of commercially available equipment, normal pancreatic echoes were simply not recognized as such.

With the superior display offered by gray-scale equipment, the margins of the pancreas and internal echoes can virtually always be visualized. However, a systematic approach must be employed. Reasoning from knowledge of the normal anatomy, it can be seen that one of the few constant features of the location of the pancreas is that it lies directly in front of the aorta and vena cava near the midline (Fig. 6). This is the underlying rationale for the initial longitudinal scanning near the mid-line. This allows identification of known echographic landmarks: *e.g.*, liver, vertebral column, inferior vena cava, and aorta. The liver, frequently being the only structure interposed between the anterior abdominal wall and the pancreatic area in the midline, serves as a relatively homogeneous medium for good transmission of the ultrasonic beam (Fig. 1). Therefore, there is no significant amount of gas to cause interference with transmission between the transducer on the skin surface and this portion of the body of the pancreas. Bowel gas occasionally presented difficulty in delineating the entire pancreatic head, necessitating a repeat examination in 16 percent of the cases in this study. The head and body were well visualized in 89 percent of normal patients in the supine position. The pancreatic tail is not well visualized in the supine position due to gas within the stomach and splenic flexure of the colon. Numerous attempts at dispelling the overlying area of gas, including ingestion of large amounts of water and administration of pharmacological agents such as simethacone, were unsuccessful. In those cases in which routine supine longitudinal scanning failed to visualize the tail of the pancreas, scanning was carried out in the prone position. This technique of scanning takes advantage of the trans-sonic nature of the normal renal parenchyma, allowing propagation of the ultrasonic beam to the tail of the pancreas, which lies just anterior to the superior pole of the left kidney (Fig. 7). This allowed imaging of the pancreatic tail

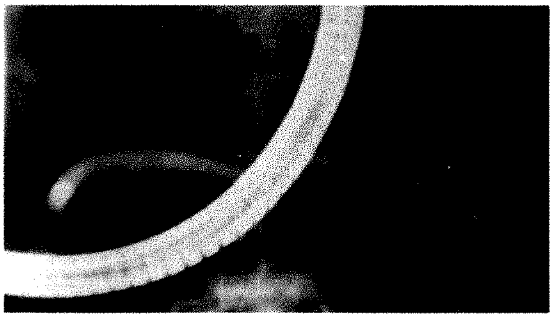

FIG. 5. Normal pancreatic ductogram in patient whose roentgenogram is shown in Figure 4.

Table I

Echographic size of the normal pancreas in cm in 382 patients ($p<0.05$)

	Head	Body	Tail
Anteroposterior measurement	2.7±0.7	2.2±0.7	2.4±0.4
Craniocaudad measurement	3.6±1.2	3.0±0.6	2.9±0.4

in 86 percent of normal subjects.

Marking the cranial and caudad limits of the pancreas on the anterior abdominal wall through the use of parasagittal scans allowed delineation of the position of that organ within the upper abdomen. Transverse or oblique scanning or both must be carried out in the long axis of these marks for adequate "transverse" imaging. Virtually all pancreases that we encountered had oblique orientations of their long axes, and could not be adequately identified by standard horizontal scanning.

Conventional roentgenograms of the wire on the patient's skin introduced geometric distortion. This was corrected by centering the central ray over the center of the pancreas, and by using a 72 inch skin-target distance.

Measurements of the pancreas in patients free of pancreatic disease were carried out in three specified anatomical areas. The pancreatic head was measured in the plane to the right of the midline in which it appeared the largest. The body of the organ was measured in the immediate pre-aortic region. The tail was evaluated in either the supine or prone position in the medial prerenal area. The dimensions of the pancreas in other areas correlated well with those obtained in these three reference planes.

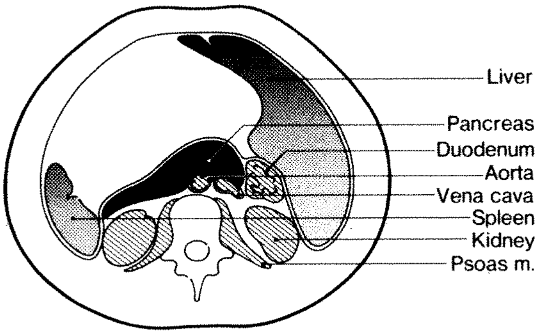

Fig. 6. Schematic representation of a transverse section through the upper abdomen to demonstrate normal anatomical relationships. Note that pancreas lies directly anterior to great vessels. Tail of pancreas lies just anterior to left kidney.

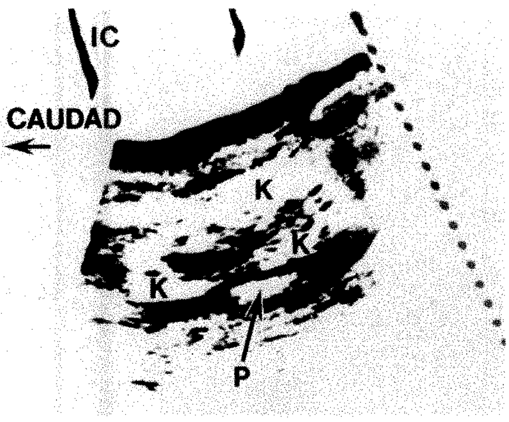

Fig. 7. Gray-scale display of normal pancreas. Prone, longitudinal scan in a plane through the medial portion of the left kidney (K). Tail of pancreas readily identified just anterior to the middle third of the kidney. Iliac crest (IC) serves as reference point.

The craniocaudad dimensions of the pancreatic head showed the greatest variation (Table 1). This was due to the large normal anatomical variation in the size and angulation of the uncinate process.

The portion of the body in the pre-aortic area was observed to be somewhat smaller in anteroposterior diameter than the adjacent body and tail. This is postulated to be due to mild compression secondary to draping of the pancreatic body over the vertebral column and aorta.

In making the measurements, it was sometimes difficult to be certain of the exact pancreatic boundaries. This was because the compounding of normal pancreatic echoes, and extraneous echoes from peri-pancreatic fat, lymphatics and vessels, produced rather thick summation echoes on the display. Because of the additive nature of these structures to the normal pancreatic outline, the values listed are likely biased on the large side by a small percentage. This offers a margin of safety in utilizing these dimensions as indices of the normal pancreas.

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INTRA- AND EXTRACEREBRAL ARACHNOID CYST*

AN ATYPICAL ROENTGENOGRAPHIC PRESENTATION

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ABSTRACT:

Arachnoid cysts present in a variety of ways, and the preoperative diagnosis usually requires a high degree of suspicion. Bony changes consistent with a chronic focal mass effect, a relative paucity of clinical findings compared to the size of the lesion, and an extracerebral mass with an intracerebral component suggest the possibility. We present a case in which there appears to be a large, deep intracerebral mass associated with an extracerebral expansion.

ARACHNOID cysts are uncommon but by no means rare intracranial lesions. Their presentation can vary from that of a progressive neurological defect[6] to an incidental finding at the time of autopsy.[14,16,20] Roentgenographically, they may mimic other conditions, particularly an extracerebral expansion such as subdural hematoma.[1,12] Rarely, the roentgenographic appearance may suggest the presence of a superficial intracerebral mass.[12] The following case of an arachnoid cyst presents an unusual roentgenographic appearance in that there appears to be a large, deep intracerebral mass associated with an extracerebral expansion.

REPORT OF A CASE

R.M., a 23 year old airman, was in good health until November 25, 1974, when he had a grand mal seizure. He was evaluated at a local Air Force hospital and found to be neurologically intact. However, routine skull roentgenograms revealed an abnormality of the sella turcica, and the patient was transferred to David Grant Medical Center (DGMC), Travis Air Force Base, California, for further evaluation.

During neurosurgical consultation at DGMC, the patient admitted having transient episodes of "blurry vision" lasting ten to fifteen seconds occurring weekly for the preceding six months, and a steady frontal headache for two weeks prior to the seizure. Review of his past medical history revealed that at age five he had fallen on a piece of barbed wire that had entered his right orbit. There had been no initial loss of consciousness, but within twelve hours he was obtunded and febrile. He was referred to the Mayo Clinic where ophthalmologic examination revealed ecchymosis of the entire right upper lid and an edematous area near the trochlea that was felt to be the site of puncture. Skull roentgenograms were normal. On lumbar puncture there was an opening pressure of 360 mm H_2O. Cell count on the cerebrospinal fluid (CSF) showed 597 lymphocytes, 3,328 polymorphonuclear leukocytes, and 20,000 red blood cells per cubic millimeter. The spinal fluid protein was 200 mgm percent and glucose was 100 mgm percent. No bacteria were seen on smear and cultures were subsequently sterile. In view of the rapid onset of symptoms and the abnormal CSF findings, the patient was treated for meningitis with parenteral and oral antibiotics for fourteen days. His recovery was uneventful and he had no further central nervous system symptoms until his grand mal seizure.

General physical and neurological examinations at DGMC were entirely normal. Opening pressure on lumbar puncture was 280 mm H_2O. CSF analysis revealed two lymphocytes per cubic millimeter, a protein of 37 mgm percent, and glucose of 58 mgm percent. Electroencephalography demonstrated two to three cycle per second delta activity in the left frontal and

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The views expressed herein are those of the authors and not necessarily those of the Department of Defense or the United States Air Force.

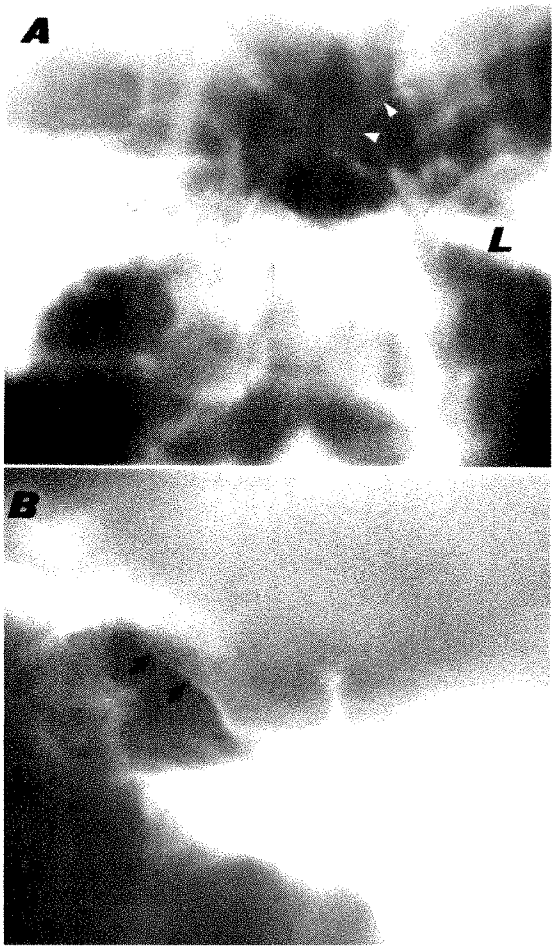

FIG. 1. (*A*) Anteroposterior tomogram of the dorsum sellae demonstrates erosion of the left lateral aspect of the dorsum and undercutting of the posterior clinoid (arrowheads). (*B*) Lateral tomogram of the sella just to the left of midline demonstrates erosion and deformity of the tuberculum sellae and chiasmatic sulcus (arrows). Note also the thinning of the dorsum. There are erosion and ballooning involving the left lateral aspect of the sellar floor.

fronto-polar regions. There was slightly diminished flow in the left frontal region on the dynamic Tc-99m study with normal static images.

Anteroposterior and lateral tomograms of the sella turcica (Fig. 1) revealed erosion affecting primarily the left lateral aspects of the floor and dorsum of the sella. In addition, there were deformity and erosion of the tuberculum sellae and the chiasmatic sulcus.

Transfemoral bilateral internal and external carotid angiography demonstrated a large, avascular, left middle cranial fossa extracerebral expansion elevating the left middle cerebral artery and displacing it and the anterior temporal artery posteriorly (Fig. 2 and 3). In addition, there were stretching and displacement of the left anterior cerebral artery and its branches, indicative of a large mass deep within the parenchyma of the left frontal lobe. The lateral ventricles appeared dilated bilaterally, the right greater than the left.

Pneumoencephalography revealed a large mass within the left frontal lobe, indenting the frontal horn of the left lateral ventricle and flattening the ventricle from side to side. The third ventricle was elevated and displaced markedly to the right, compressing the right foramen of Monro so that the right lateral ventricle did not fill with air. The left temporal horn and subarachnoid spaces of the left middle and anterior cranial fossae failed to fill, and there was no filling of the subsequently proved cyst.

At craniotomy, the anterior aspect of the left frontal bone was quite thin. Upon opening the dura, the underlying brain was swollen but pulsatile. The gyri were flattened but the sulci were not appreciably narrowed. The frontal

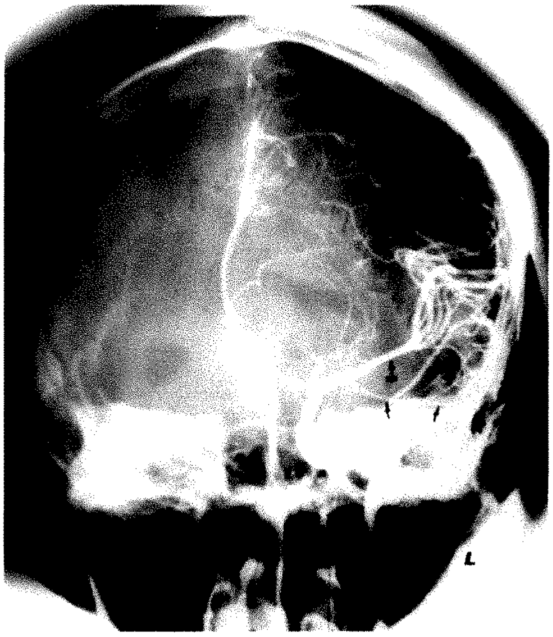

FIG. 2. Anteroposterior view during left internal carotid artery injection demonstrates elevation of the horizontal segment of the left middle cerebral artery (double crossed arrow) by the extracerebral component of the cyst. There is stretching of the anterior temporal artery and its branches (arrows).

pole was cannulated, and at a depth of one centimeter a cystic cavity was entered which contained clear fluid. Through a cerebrotomy incision the cyst was inspected. The dome of the cyst abutted on compressed gyri which represented the base of the left frontal lobe. The appearance was that of an entirely extracerebral lesion indenting the brain. Following partial decompression of the cyst, the frontal pole was retracted from the floor of the anterior fossa, allowing direct visualization of the entire cyst (Fig. 4 and 5). It filled the major part of the left frontal fossa to the midline and extended over the sphenoid ridge into the anterior portion of the left middle fossa. The left temporal lobe was displaced posteriorly, exposing the insular cortex. The entire course of the horizontal segment of the left middle cerebral artery was visualized and found to be displaced posteriorly and superiorly. The horizontal segment of the left anterior cerebral artery was bowed medially across the midline, as were the left optic nerve and infundibulum, by loculations of the cyst in the left parasellar region. The volume of the entire cyst was estimated at 250 cubic centimeters. The arachnoid lining was thickest as it reflected from the floor of the anterior fossa onto the brain. Communications were made between the parasellar loculations, the main body of the cyst, and the chiasmatic cisterns. Septae in the middle fossa portion of the cyst were disrupted to insure free communication between the middle and anterior fossa components. Portions of the cyst lining were excised and sent for histological examination.

Microscopic sections of the wall of the cyst that abutted on the cortex revealed gyri and non-specific connective tissue. Sections of the cyst wall from the floor of the anterior cranial fossa demonstrated thickened leptomeninges with occasional clusters of mononuclear inflammatory cells and a few polymorphonuclear leukocytes. There was no evidence of hemosiderin within any of the cells.

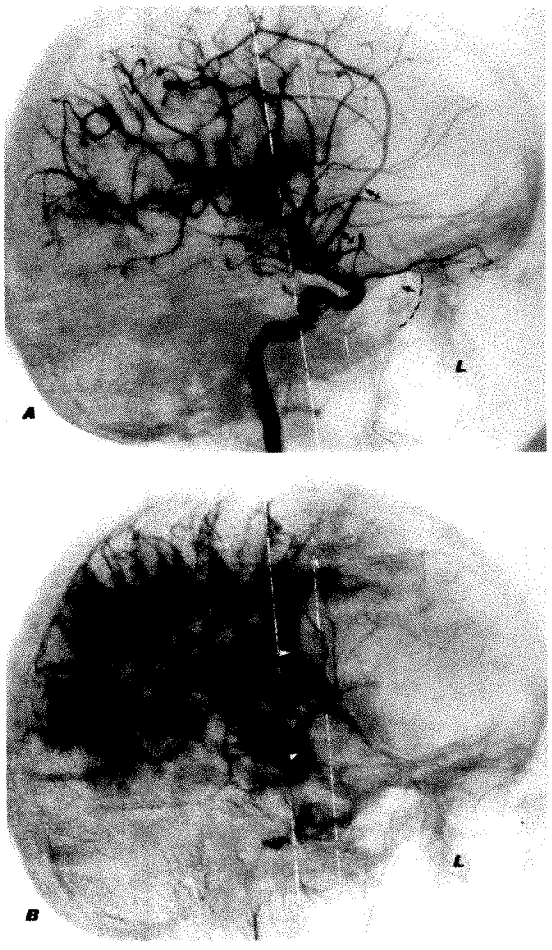

Fig. 3. Lateral views during left internal carotid artery injection. (*A*) The arterial phase demonstrates stretching and posterior displacement of the horizontal segment of the left middle cerebral artery (double crossed arrow). An anterior temporal artery branch (arrow) is displaced posteriorly from the anterior wall of the left middle cranial fossa (dashed line), indicative of the extracerebral mass within the left middle cranial fossa. There are stretching and posterior displacement of the proximal portion of the left anterior cerebral artery (single crossed arrows) and stretching of multiple anterior cerebral artery branches by the intracerebral component of the cyst. (*B*) The early venous phase demonstrates a large area of relative lucency within the left frontal lobe and stretched superficial veins outlining the intracerebral component of the cyst (arrowheads).

DISCUSSION

Arachnoid cysts have been described as occurring within the posterior fossa subarachnoid spaces,[8,10,20] over a cerebral convexity,[1,2,5–7,12,16,19] between the cerebral hemispheres,[11,20] within the Sylvian fissure,[1,2,4,13,14,17,18] in the suprasellar region,[4,8,20] or within the quadrigeminal and ambient cisterns.[8,9,20] These cysts generally appear to be entirely extracerebral in location on roentgenographic examination. Rarely, the brain may be locally indented

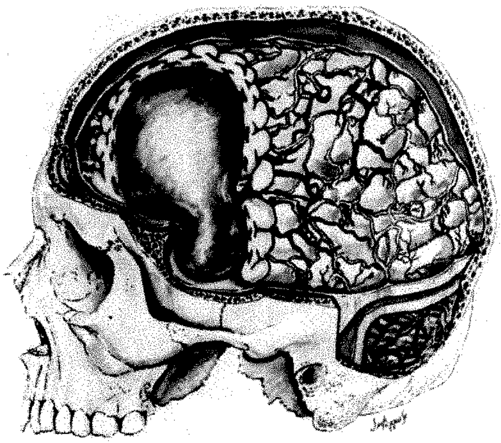

FIG. 4. Schematic drawing in lateral projection with cut-away of portions of the left frontal and temporal lobes. The cyst not only occupies the anterior aspect of the left middle cranial fossa but also dramatically indents the left frontal lobe.

in such a manner that contrast studies suggest the presence of a superficial avascular intracerebral mass associated with an extracerebral expansion.[12] The cyst in our case indented the base of the left frontal lobe to such a degree that only thin rims of cortex and a small amount of compressed white matter separated the dome of the cyst from the superior aspect of the brain. This resulted in the unusual roentgenographic appearance of a large avascular intracerebral expansion deep within the frontal lobe contiguous to an extracerebral expansion within the left middle cranial fossa.

Arachnoid cysts are said to be either congenital in origin or secondary to such factors as trauma, hemorrhage, or infection. There are numerous well-documented cases of congenital cysts, many of which present in infancy.[1,2,4,8,9,11,14,18] There are fewer cases with good documentation of antecedent infection,[3,10,14] hemorrhage,[7,10,16] or trauma without fracture.[7,16,17] We feel in this case that the penetrating injury and probable meningitis were the contributing factors for the development of the acquired arachnoid cyst. Localized hemorrhage at the site of trauma, or purulent meningitis, may lead to adhesions with loculations of the subarachnoid space and subsequent cyst formation.[7,10,13,15,16,17]

The preoperative diagnosis of an arachnoid cyst generally requires a high degree of suspicion. There are no pathognomonic features for this entity. However, the triad of (1) bony changes consistent with chronic focal mass effect;[5,13,16,19] (2) a relative paucity of clinical findings compared to the size of the lesion;[2,16] and (3) an extracerebral mass with an intracerebral component[12] should strongly suggest the possibility of an arachnoid cyst.

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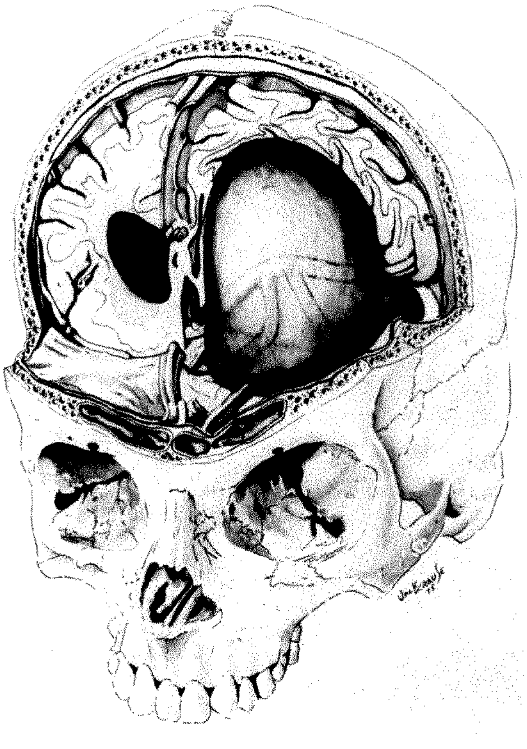

FIG. 5. Schematic drawing in anteroposterior-oblique projection with cut-away of portions of the frontal lobes. The cyst elevates the cortex of the base of the left frontal lobe as it indents the brain.

Illustrator, Travis Air Force Base, California, for his fine work in the preparation of the drawings for this manuscript.

ADDENDUM:

Since the submission of this paper for publication, one of the authors (R.E.L.) has seen two additional examples of an apparent intracerebral mass at angiography produced by a totally extracerebral arachnoid cyst invaginating into brain. In one of the cases, a computerized transaxial tomographic scan suggested the correct diagnosis.

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RADIATION-INDUCED RENOVASCULAR HYPERTENSION*

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ABSTRACT:

Radiation is known to produce changes in the small vessels and interstitium of the kidneys resulting in hypertension. Two cases of renal artery stenosis and resultant hypertension secondary to abdominal irradiation are reported and the literature is reviewed.

RADIATION may produce irreversible changes in the small vessels and interstitium of the kidneys resulting in hypertension and chronic renal failure.[12,14,20] Although there are reports of radiation damage to large arteries, to our knowledge there are no reports of renal artery stenosis secondary to radiation-induced atherosclerosis. The following cases of renal artery stenosis and resultant hypertension were induced by abdominal irradiation. This is a potentially correctable cause of radiation-induced hypertension that should be distinguished from radiation nephritis.

REPORT OF CASES

CASE I. W. A. is a 27 year old male who was admitted to the University of Virginia Hospital with a three month history of severe headaches, dizziness, and blurred vision. There was no past history of renal disease nor family history of diabetes or coronary artery disease. He had received 3,276 rads to the retroperitoneal region 12 years prior to admission for a malignant anaplastic tumor with masses of nodes extending from the renal pedicles to the undersurface of the liver. Subsequent reports from the Armed Forces Institute of Pathology and the University of Virginia described the tumor as a retroperitoneal reticulum cell sarcoma. The treatment was delivered in 22 fractions over a period of 25 days, treating only one field per day and employing a 250 kV conventional unit. The nominal standard dose (NSD) was estimated to be 1,095 rets.

His blood pressure was 200/150. The blood urea nitrogen level was 64 mg percent and the creatinine was 2.5 mg percent. The intravenous pyelogram showed a small right kidney with delayed and decreased function. The left kidney was normal in size. A midstream renal arteriogram demonstrated bilateral renal artery stenosis more marked on the right (Fig. 1).

At surgery extensive adhesions in the upper abdomen were present and thought to be secondary both to the previous exploratory laparotomy and to irradiation. No retroperitoneal masses were noted. Exploration of the renal arteries revealed well-localized atherosclerotic changes confined to the proximal portions of the renal arteries. There was also subintimal atheromatous change of the abdominal aorta in the area of the renal arteries, but not in the region of the aortic bifurcation, which was outside the treated volume.

Bilateral endarterectomies and bilateral aortorenal bypass grafts were performed. The right graft clotted, and satisfactory arterial flow to the kidney was never established, necessitating a right nephrectomy. The predominant histologic changes in the right kidney were felt to represent ischemic atrophy.

Postoperatively the patient remained in renal failure, and four months later it was necessary to remove his left kidney due to thrombosis of the graft and to place him on renal dialysis. His blood pressure returned to normal after the nephrectomies.

CASE II. L.W. is a 33 year old male who was admitted for evaluation of hypertension of recent onset. His past history was remarkable in that he had a left orchiectomy for seminoma six years prior to admission. Postoperatively he was treated with irradiation to the left pelvis and periaortic nodes. The field included his renal arteries. He received 3,744 rads in 18 fractions at three day intervals over a period of 38 days. The treatment was carried out with a cobalt 60 unit, and the estimated NSD was 1,254 rets.

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On physical examination his blood pressure was 180/122. His eye grounds revealed pinpoint hemorrhages, waxy exudates, arteriolar spasm, and arteriovenous nicking. His blood urea nitrogen level was 20 mg percent and creatinine 2.0 mg percent. The renal vein renin levels were: peripheral, 7.05 nanograms/ml/hr incubation; right kidney, 8.54 nanograms; left kidney 11.92 nanograms. Renal arteriography revealed severe stenosis of the left renal artery (Fig. 2).

At operation there were changes of the aorta compatible with the previous irradiation. An atheromatous plaque was present at the origin of the left renal artery. An endarterectomy and saphenous vein patch graft were performed on the left renal artery. Needle biopsies were obtained of both kidneys since the perirenal fatty tissue was indurated and extremely vascular. Both renal biopsies showed moderate focal arterial and arteriolar sclerosis and focal interstitial fibrosis. These findings were felt to be consistent with left renal artery stenosis. There was no evidence of radiation nephritis.

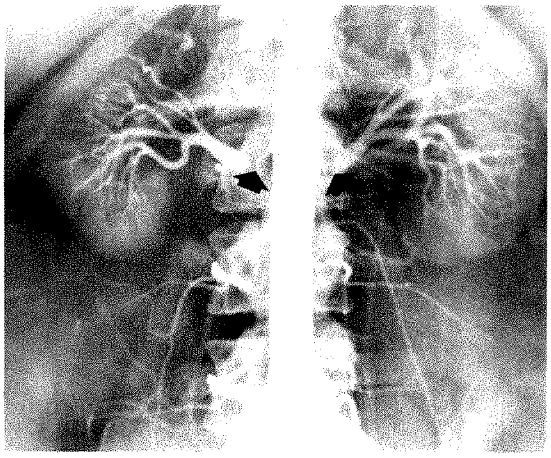

FIG. 1. Midstream renal arteriogram demonstrates bilateral renal artery stenosis (arrows). The stenosis on the right is more severe than the stenosis on the left.

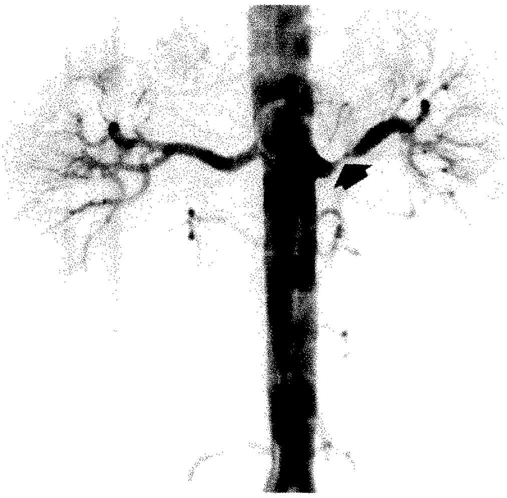

FIG. 2. Subtraction film of midstream renal arteriogram demonstrates a stenosis of the proximal left renal artery (arrow).

Postoperatively the patient's hypertension was easier to control. His blood pressure was 140/100 while taking Aldomet 250 mg twice each day and Hydrochlorothiazide 50 mg daily. Postoperatively his blood urea nitrogen level measured 21 mg percent and creatinine 0.9 mg percent.

COMMENT

Experimental evidence indicates that irradiation may produce damage to large arteries.[1,2,7,9–11] In addition to experimental documentation of radiation-produced large artery damage, there are also numerous reports of radiation-produced arterial damage seen either at autopsy or demonstrated arteriographically. Poon *et al.*[15] described necrotizing aortitis with rupture as a complication of mediastinal irradiation. Histologically, fragmentation of the elastic fibers was seen at the point of rupture. There was also marked alteration of the media of the irradiated thoracic aorta as well as thickening of the intima and adventitia.

Marcial-Rojas and Castro[13] reported autopsy findings on eleven patients who died of hemorrhage secondary to rupture of large arteries after radiation therapy. The morphologic changes were sharply limited to the vessels directly in the field of radiation. It should be noted that a common feature of all of these cases of acute hemorrhage was the presence of associated infection in the irradiated areas.

Thomas and Forbus[19] observed thickening of the wall of the aorta and alterations of the intima resembling those seen in syphilitic aortitis. These gross as well as microscopic changes in the intima, media, and adventitia were confined to the segment of the aorta within the field of radiation.

Colquhoun[4] reported hypoplasia of the abdominal aorta and renal arteries discovered in two patients three and 13 years after abdominal irradiation received as infants. Benson[3] recently described three cases involving injury of the right subclavian artery, both external iliac arteries, and a left superficial femoral artery discovered at 3, 28, and 30 years, respectively, after irradiation for neoplasms. Hayward[8] reported premature atherosclerosis in the great vessels of the neck discovered 27 years after external irradiation of the thyroid.

Dencker *et al.*[5] described the angiographic findings in six patients with occlusive disease of the superior mesenteric and inferior mesenteric arteries and their branches occurring from 4 months to 17 years after pelvic irradiation for neoplasms.

Savlov *et al.*[18] reported severe bilateral localized femoral and iliac atherosclerosis found two years after pelvic and abdominal irradiation for a right ovarian papillary adenocarcinoma.

Tracy *et al.*[21] and other authors[6,16] have observed coronary artery disease in young patients after mediastinal irradiation. The age of these patients, their normal cholesterol levels, and the temporal relationship to irradiation of the chest make radiation-induced arteriosclerosis the probable etiology.

Radiation injury has been shown to produce stenosis of large arteries by several mechanisms. Atherosclerosis may be induced with a resultant decrease in the cross-sectional area of the arterial lumen. Luminal narrowing can be produced by increased collagen deposition in the intima by proliferating fibroblasts. Stenosis may also be produced by fibrosis either as a reparative response to radiation damage or as a consequence of radiation injury of the vasa vasorum of the vessels.[17]

Any one or combination of the above mechanisms may produce arterial stenosis. In our cases, atheromatous plaques were found in the renal arteries. This suggests that premature atherosclerosis was the cause of the stenoses. Since the patients were 27 and 33 years old with no family history of early atherosclerotic disease, the question arises as to the role irradiation played in the etiology of the premature atherosclerotic changes.

To attribute vascular damage to irradiation, certain criteria must be considered. First, it is necessary for the alterations to be within the field of irradiation as evidenced in both of our cases. The changes in the first case were bilateral. It initially may appear that the unilateral stenosis in the second patient is an argument against irradiation damage; however, the stenosis was caused by an atheromatous plaque in the proximal renal artery. Second, the level of the dosage and whether the tolerance of the normal tissues has been exceeded need to be considered. Many cases of seminoma receive 3,000 rads in 15 treatments over a period of three weeks, an NSD of 1,126 rets. The dosage levels in our cases of 1,095 rets and 1,254 rets do not appear to be significantly different from this. It must be noted that many cases of Hodgkin's disease and non-Hodgkin's lymphoma receive substantially more irradiation to the periaortic nodes without these complications. Although the dosage levels in our cases were comparatively low, it is felt that irradiation contributed to the premature atherosclerotic findings since the damage was limited to the radiation field.

The clinical course suggests that renal artery disease was the cause of hypertension in our cases. In the first case the blood pressure returned to normal after the kidneys were removed. In the second case significant reduction in the severity of his hypertension was achieved after normal blood flow to the left kidney was surgically reestablished.

It is our feeling that renal arteriography should be considered in all patients who become hypertensive at any time after abdominal radiation therapy. We recognize that in some cases the hypertension will be due to renal parenchymal and small vessel damage or will represent essential hypertension. We feel, however, that a significant number of these patients will have renal artery stenoses which may be correctable.

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POSTESOPHAGEAL NARROWING ASSOCIATED WITH BARRETT ESOPHAGUS*

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ABSTRACT:

Two children have been found to have partially obstructing lesions beyond the esophagus in association with mid-esophageal stricture. Both were found to have columnar epithelium-lined (Barrett) esophagus, and gastro-esophageal reflux. The more distal obstruction, in the pylorus and descending duodenum respectively, may have contributed to the development of the Barrett esophagus. It is recommended that any barium study of the esophagus which reveals an unexplained stricture should include visualization through the duodenojejunal junction as an aid to diagnosis, management, and understanding.

DESPITE increased recognition of the columnar epithelium-lined lower esophagus described by Barrett in 1950,[1] there has not been emphasis on associated findings beyond the esophago-gastric junction. Fluoroscopic evaluation of the stomach and entire duodenum should be part of the radiographic study of any patient with this condition, in order to plan adequately the course of management. In addition, findings in our study of two patients may contribute to understanding the etiology of some cases of Barrett esophagus.

REPORT OF CASES

CASE 1. R.W., a 14 year old boy, had experienced intermittent dysphagia, mostly with solid foods, for five years. There was no definite history of caustic ingestion and no gastrointestinal surgery. A barium esophagogram showed a stricture at the junction of upper and mid esophagus (Fig. 1). Unfortunately, the stomach and duodenum were not observed at that time. The patient underwent esophagoscopy which confirmed the stricture. The esophagus was dilated to the diameter of a No. 26 French catheter. Three months later esophagoscopy and dilatation were repeated.

A year after the second dilatation the patient still had occasional vomiting.

At follow-up roentgen examination, barium was followed to the ligament of Treitz. In addition to demonstration of hiatus hernia, abnormality was seen more distally. A moderately narrow pylorus was surrounded by a prominent soft tissue mass which had ovoid margins on all views. This soft tissue structure indented the barium-filled distal stomach in the manner

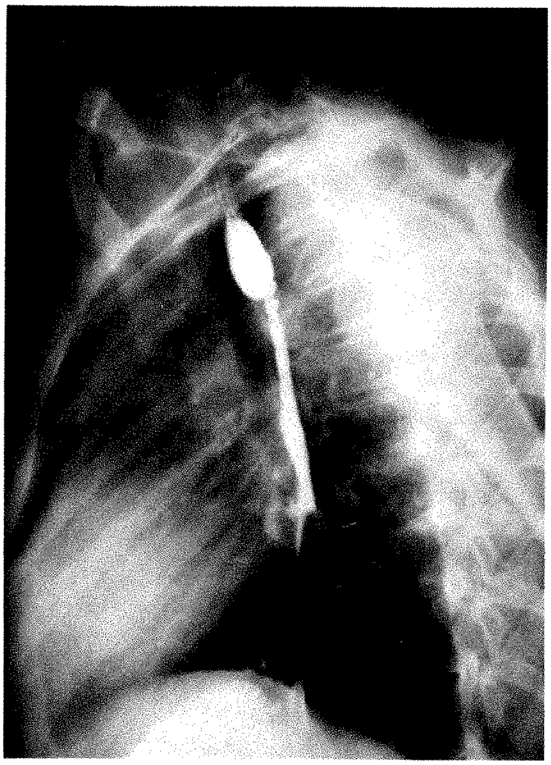

FIG. 1. Case 1. Stricture in upper mid-esophagus at the interface between squamous and columnar epithelium lined esophagus. Above and below this zone the esophagus behaved normally.

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typical of hypertrophic pyloric muscle of infancy (Fig. 2; and 3).

Esophagoscopy showed the stricture 25 mm beyond the incisors. There was a sharp demarcation of mucosa at that level. Esophagitis was seen just above this line. A biopsy just beyond the line showed gastric columnar epithelium. The histological diagnosis was Barrett esophagus.

In view of all the findings, the patient underwent additional mid-esophageal dilatation and then a fundoplication, hiatal herniorrhaphy, vagotomy, and Heineke-Mikulicz pyloroplasty. During the operation, the pylorus was observed to be tight and did not relax over a period of observation. The patient has gradually improved since surgery.

CASE II. D.E. was a nine year old boy who suddenly developed dysphagia. Except for occasional cough for three months he was previously believed to be in good health. For a brief period in infancy, however, he was said not to "eat well." There was no known history of caustic ingestion, and no prior surgery. He arrived at our medical center following one day of discomfort. An esophagogram at another office was said to show an obstructed mid-esophagus. The stomach and duodenum were apparently not studied. Physical examination was normal. Esophagoscopy at our institution revealed a grape lodged in the mid-esophagus; this region was dilated to the size of a No. 20 French catheter upon removal of the foreign object.

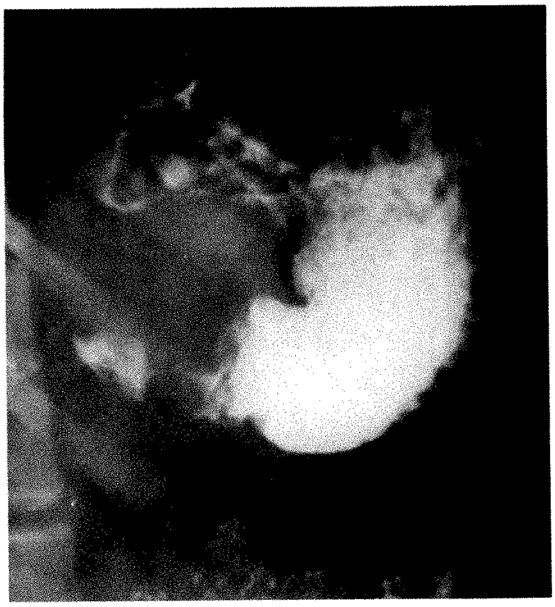

FIG. 2. Case I. The pylorus is narrow and there is a shoulder sign of pyloric muscle upon the antrum.

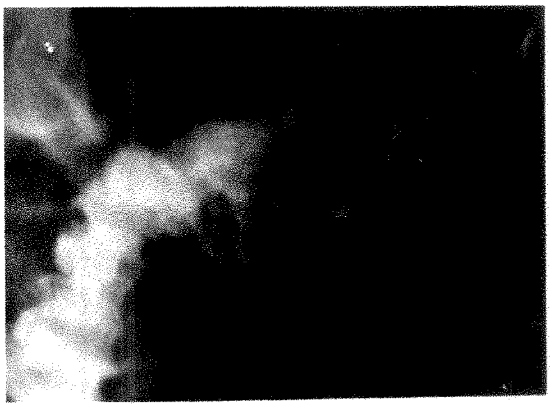

FIG. 3. Case I. A close-up of the region shows persistence of the abnormalities; the pyloric muscle did not relax when observed at subsequent laparotomy.

The post-procedure barium study no longer showed an esophageal stricture. However, despite the denial of gastrointestinal symptoms since the episode of the grape, the study was continued beyond the esophagogastric junction. Beyond the normal pylorus was a marked dilatation of the proximal half of the duodenum, through the descending portion (Fig. 4). A normal distal duodenum and ligament of Treitz localization were noted. Erect film study indicated rather marked retention of fluid density material in the widened segment (Fig. 5). Follow-through examination indicated no malrotation of bowel. Annular pancreas, duodenal stenosis, or both, were thus considered the most likely possibilities.

Six weeks later an annular pancreas was found at laparotomy. A duodenojejunostomy was performed to bypass the zone of narrowing. The patient was then symptom-free for about a month, when dysphagia and painful swallowing recurred. An esophagogram indicated stricture of the esophagus.

At esophagoscopy, the stricture was at 18 cm from the incisors. Biopsy at 18–19 cm revealed gastric type mucosa. The region was dilated. The following month motility studies revealed an absence of the physiological lower sphincter of the esophagus. The patient underwent Nissen fundoplication at his esophagogastric junction. He has done well since then.

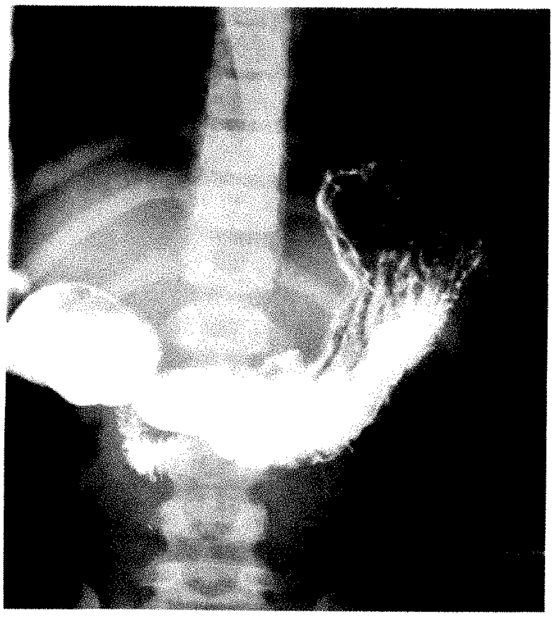

FIG. 4. Case II. Overhead film showing greatly dilated proximal duodenum and normal distal duodenum.

Comment. In our first patient a year elapsed before any abnormality beyond the esophagus was suspected or detected. Discovery and treatment of the non-relaxation of pyloric muscle resulted from completing the barium study through the duodenum. Similarly, quite a pronounced partial obstruction of the duodenum was noted in the second patient only when the region beyond the esophagus was radiologically screened. In both patients the diagnosis of Barrett esophagus was also delayed.

DISCUSSION

In considering Barrett esophagus, several pathophysiological points should be reviewed. The distal portion of the esophagus, usually more than half its length, contains a columnar epithelium typical for stomach. There are normal esophageal muscle and peristalsis pattern in the same distal esophagus, except for sites of ulcer or stricture. The proximal esophagus contains the usual squamous esophageal epithelium. Stricture, often several cm long, generally occurs at the junction of the two types of epithelium. Esophagitis is often seen in the esophagus above the junction interface and may be a precursor of the stricture. Barrett ulcer represents a peptic ulcer in the columnar lined portion. There appears to be increased incidence of malignancy in the Barrett esophagus.[5]

If Barrett esophagus is an acquired condition, as is currently held by many investigators,[3] it becomes relevant to follow the barium to the ligament of Treitz to seek reasons for the transformation of the mucosa. Hiatus hernia or absence of physiological lower esophageal sphincter can be responsible for repeated bathing of the lower esophagus with gastric contents, leading to esophagitis. Transformation of healing esophageal epithelium to the gastric columnar form may be a defense mechanism in this situation. The additional presence of a more distal partial obstruction could greatly encourage such reflux. In the typical Barrett esophagus patient, the interface between squamous and columnar epithelium is indeed in the upper half of the

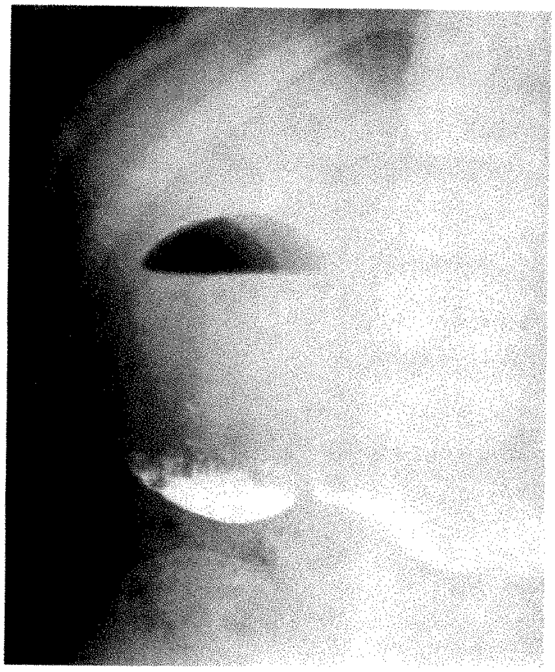

FIG. 5. Case II. Erect film shows air above retained fluid and barium caused by narrowing at the subsequently surgically-confirmed annular pancreas site.

esophagus, as in our patients. If that represents a response to reflux, that reflux must have been quite severe, which is a reason for seeking any more distal obstruction.

Although Barrett esophagus has been reported principally in adults, there have been several pediatric cases.[1,7,9] The final case illustration in Barrett's classic article was 13 years old.[1] A neonatal autopsy specimen has shown an esophagus nearly totally lined with columnar epithelium.[8] The more distal obstruction is apparently not a necessary component for development of Barrett esophagus in all patients. Franken's patient had a normal esophagogram in infancy, then developed Barrett esophagus by seven years of age.[7] In the report by Visalli of a child with Barrett esophagus, the illustrated roentgenogram shows normal stomach, pylorus, and entire duodenum.[9]

Regardless of the etiologic role of the more distal obstruction, its association with the columnar epithelium-lined esophagus is important whenever present. Endoscopic or surgical treatment limited to the mid-esophageal segment is incomplete if a more distal obstruction is not also treated. Hence, the observation of antrum, pylorus, and duodenum should be part of the initial esophageal roentgen study. It should be noted that most cases of Barrett esophagus reported in the literature do not have any comment as to the status of the upper gastrointestinal tract beyond the esophagogastric junction. Such information would help decide the relative frequency of more distal obstruction.

Clinical history and physical examination, as well as the esophageal barium examination proper, may serve to distinguish other causes of mid-esophageal narrowing from the Barrett syndrome. Among these entities are prior caustic ingestion with stricture, the sequelae of repair of esophageal atresia, the site of ectopic tracheobronchial mucosa,[6] association with intramural diverticulosis,[10] and as part of more generalized cutaneous disorders, such as epidermolysis bullosa.[7] A recent report described a case of an esophageal mucosal diaphragm resulting in a stricture.[4] If the underlying diagnosis is not clear, the discovery of a partially obstructing lesion distal to an incompetent esophagogastric junction ought to encourage appropriate esophageal biopsy or nuclear imaging study[2] for consideration of columnar epithelium-lined esophagus as a diagnosis.

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MULTICHAMBERED BLADDER ANOMALIES*

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ABSTRACT:

This report reviews multichambered bladder conditions, offers a workable classification of them, presents a detailed case report, and discusses the possible causes of these anomalies. We wish to stress the importance of careful examination of the genital area in the newborn and early roentgenologic evaluation of the genitourinary system when an anomaly is found.

DEVELOPMENT of the bladder into multiple chambers is uncommon but potentially serious. Such cases may be accompanied by anomalies of the kidneys, urethra, genital organs, external genitalia, colon, rectum, and anus.[8,9]

The following report (1) discusses a patient with a multichambered bladder anomaly and unilateral renal agenesis and (2) reviews and illustrates the various types of anomalies.

REPORT OF A CASE

On October 10, 1973, a 7 month old Black female presented with recurrent urinary tract infections since 2 months of age. The birth and neonatal period were uncomplicated. Except for a single opening between the labia, the physical examination was unremarkable. The anus appeared normal.

An intravenous urogram showed no excretion on the left. The right kidney appeared normal and its ureter emptied into the medial aspect of the bladder structure which was markedly deviated to the right by a midline pelvic mass (Fig. 1). The midline mass was filled with dilute contrast medium when the patient voided spontaneously during fluoroscopy.

At cystoscopy a catheter was passed directly into the midline pelvic structure through the single opening between the labia (Fig. 2*A*). Another catheter was inserted into the right sided bladder structure which drained the right ureter (Fig. 2*B*). This examination showed that although the two chambers do not directly communicate, they are inferiorly associated and drain through a common channel to the outside *via* the single orifice between the labia (Fig. 3). When a small vaginal opening was found on the posterior surface of this common channel, injection of contrast medium into this orifice showed an elongated vagina (Fig. 4). The common channel represents a urogenital sinus.

An exploratory laparotomy on October 15, 1973 confirmed the absence of the left kidney and ureter. A small uterus with tubes and ovaries was on top of the elongated vagina. No

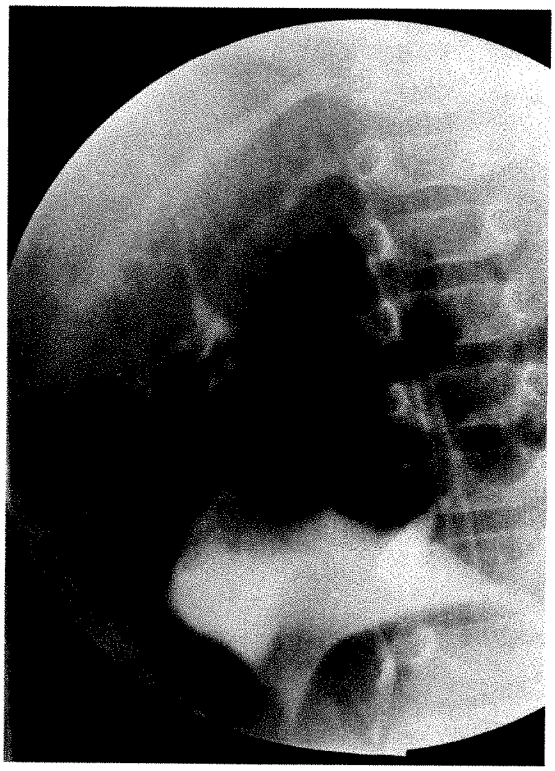

FIG. 1. Intravenous urogram demonstrating a normal right kidney with a contrast medium filling a portion of bladder seen on the patient's right.

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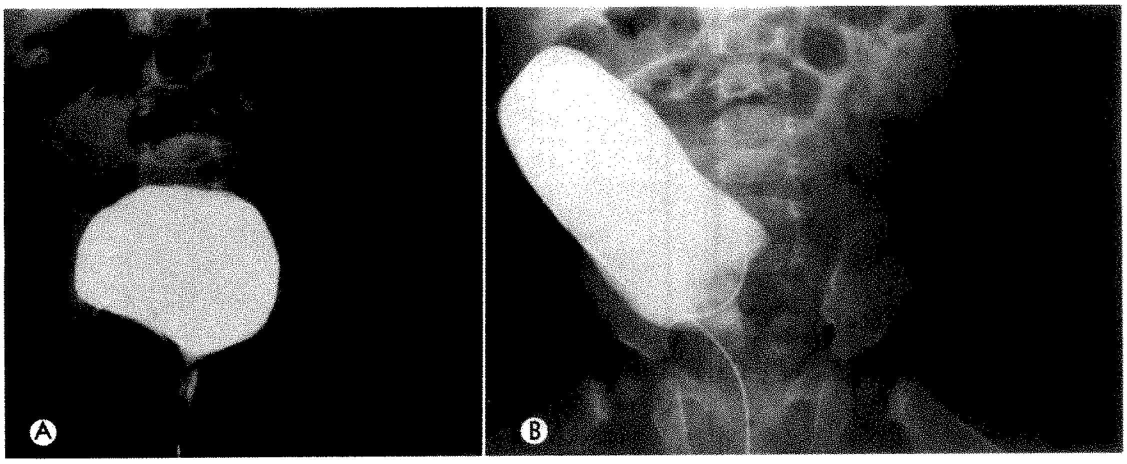

Fig. 2. Retrograde cystogram. Catheter injections in that portion of bladder in the midline (*A*) and on the patient's right (*B*). The ureter emptied into the right-sided structure.

peritoneal fold separated the 2 bladder chambers. The majority of the midline bladder structure was surgically resected since this chamber was a urine reservoir contributing to the urinary tract infections. The chamber draining the right ureter was left intact.

Histological sections of the resected chamber showed the presence of smooth muscle and transitional epithelium with areas of squamous metaplasia and early changes of cystitis cystica.

Follow-up intravenous urograms and cystograms of the remaining structures have shown interval growth of the right kidney which remains normal except for compensatory hypertrophy and no evidence of vesico-ureteral reflux. Renal function studies have remained normal. The child did have a urinary tract infection in early 1975. Calibration suggested that the common channel was stenotic causing post-voiding residual urine. She responded well to antibiotics and dilatation of the common channel.

DISCUSSION

A classification of congenital compartmentalization of the bladder we use is as follows:

1. Sagittal Division.
2. Frontal Division.
3. Multiseptated Bladder.
4. Hour-glass Bladder.
5. Congenital Diverticula.
6. Urachal Anomalies.

Sagittal Division. There are four varieties. (a) Complete reduplication of the bladder occurs when there are two bladders, lying side-by-side and each drains through a separate urethra. The walls of the bladders are separated by a peritoneal fold of varying depth and consist of mucosal and muscular layers. Each bladder receives a ureter from the ipsilateral kidney. Various reports of this anomaly[1,6,8,9] show that associated duplications of the genital and distal gastrointestinal tracts and external genitalia are frequent. Rectal atresia, stenosis,

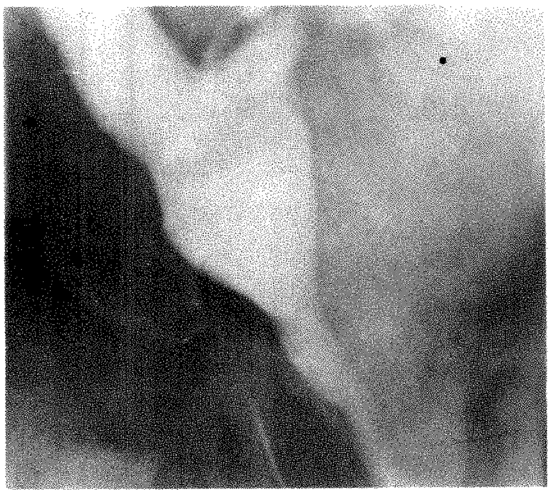

Fig. 3. Voiding cystourethrogram showing the urogenital sinus exiting through the solitary opening between the labia.

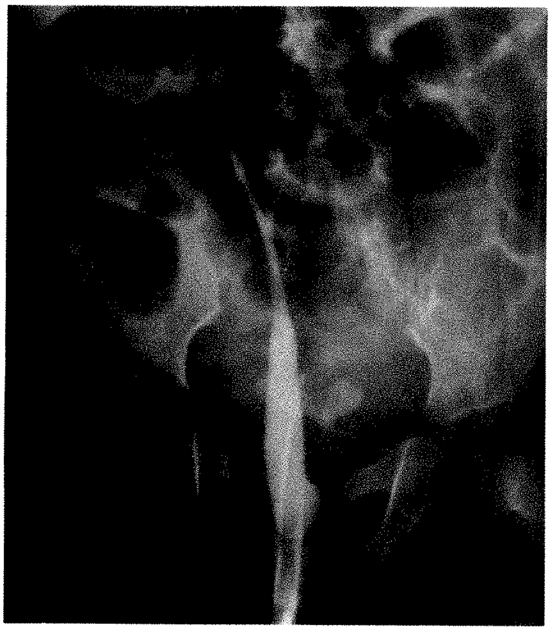

FIG. 4. Retrograde injection of a thin elongated vagina that emptied into the posterior wall of the urogenital sinus.

ectopia, and other cloacal abnormalities of development are often present. Duplication of the spine occurs less commonly. (b) Incomplete reduplication is less common than complete reduplication[1,4] (Fig. 5). The bladders lie side-by-side and are separated by a peritoneal fold of varying depth and each side receives the ipsilateral ureter. However, the bladders join at their lower ends and empty through a common urethra. There is a much lower incidence of accompanying anomalies. (c) Complete sagittal septum of the bladder occurs when a sagittal septum, which may be muscular, mucosal, or both, separates the bladder into two equal or unequal chambers. Only one side usually communicates with the urethra and therefore if the obstructed side drains a functioning kidney, that kidney is hydronephrotic, aplastic, or hypoplastic. The distended blind chamber may obstruct the opposite one. (d) In the incomplete sagittal septum there is a defect in the lower end of the septum resulting in communication of the two separate chambers.

Frontal Division. (a) Incomplete frontal septa divide the bladder into anterosuperior and posteroinferior chambers. The ureters open into the posteroinferior chamber. (b) Complete frontal septation is rare. Singh *et al.*[8] in 1973 reported a case of complete frontal septation of the bladder with two separate urethrae in a 6 month old boy. The ureters opened to the posterior bladder structure. The urethra draining the blind anterior bladder was located in front of the functioning urethra and opened to the dorsum of the penis in its midportion. There was apparently no peritoneal fold separating the bladders.

Multiseptated Bladder. Externally the bladder appears normal, but internally it is divided by septa into multiple communicating chambers. If one excludes multiple diverticula, then this anomaly is quite rare. Kohler[3] reported this condition in a 10 day old infant in 1940.

Hour-glass Bladder. The bladder is constricted into two chambers one above the other. The division occurs at any level above or below the ureteric orifices, and

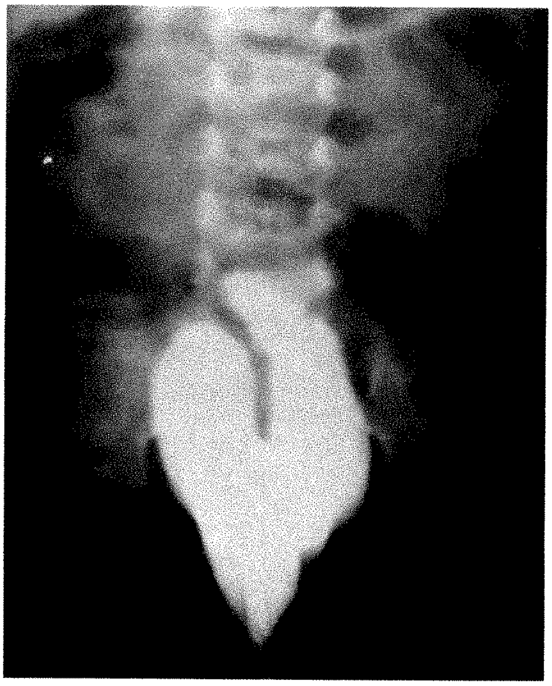

FIG. 5. An infant girl with incomplete reduplication of the bladder showing the 2 bladders that join distally.

the degree of constriction varies. Because either a urachal diverticulum or a dilated posterior urethra due to posterior urethral valves might simulate an hour-glass bladder, these must be differentiated. An hourglass bladder must be normal above and below the constriction.

Congenital Diverticulum of the Bladder. Schiff and Lytton[7] found 26 cases of solitary vesical diverticulum in children without intravesical obstruction and added three additional cases. There may be multiple diverticula. They claim that the diverticular wall may contain mucosa and muscle fibers, but the latter may be replaced by fibrosis from inflammatory changes. The differentiation between a congenital and an acquired diverticulum may be difficult. We assume a large diverticulum is congenital in an infant or child whose bladder and urethra are otherwise normal. We have seen eight patients with such bladder diverticula (Fig. 6).

Urachal Anomalies. The communicating urachal diverticulum is not uncommon and the diagnosis is usually not difficult (Fig. 7).

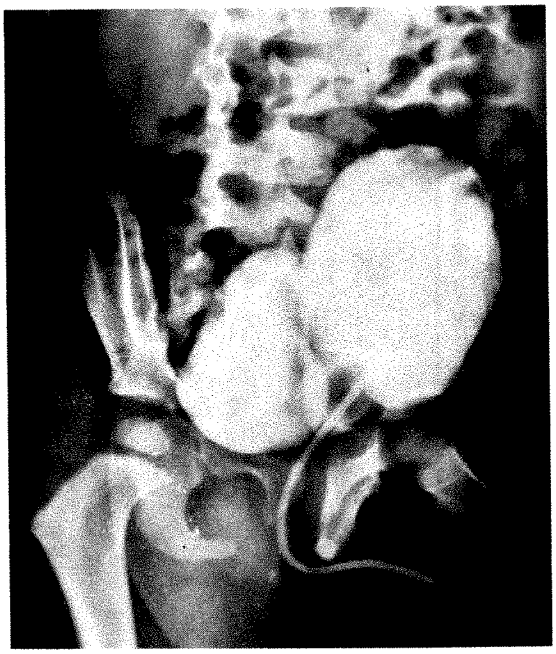

Fig. 6. A boy with a right-sided congenital bladder diverticulum that eventually required surgical removal. No other abnormalities were present.

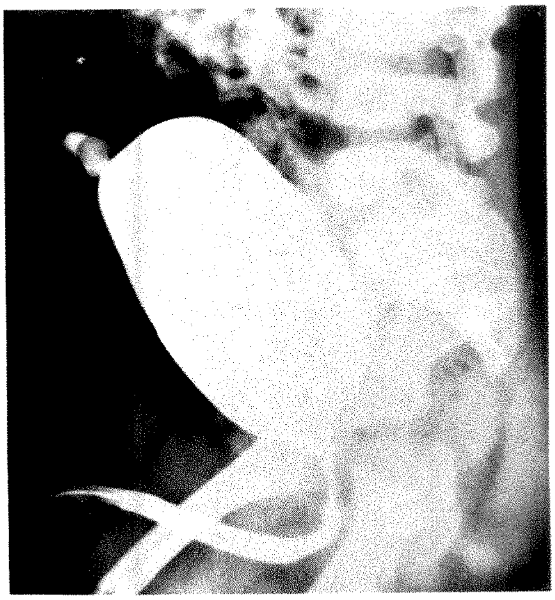

Fig. 7. A boy with a urachal diverticulum. The sacrum is hypoplastic. The posterior urethra was normal on other roentgenograms.

Although many embryologic explanations of these anomalies have been offered, no one theory explains them all.

The high incidence of associated duplication of the colon, genitalia, and spine with complete duplication of the bladder is probably best explained by Ravitch[5] as a form of partial twinning that occurs within the first two weeks of embryonic life. Abrahamson[1] postulates that the twinning stimulus is weaker when such anomalies as incomplete reduplication and complete and incomplete sagittally septated bladders occur. He also feels that frontal septa and multiseptated bladders may have different causes: (1) a possible relation to an aberrant urorectal septum or (2) persistence of the fused portion of the urogenital sinus and mesonephric ducts. The hourglass bladder is closest to a separate entity and has not had an adequate embryologic explanation.

Since a congenital bladder diverticulum is most often located just superior to the ureteral orifices, this condition may be related to an exaggerated weakness of the musculature in these regions.[2,7]

The case presented in this paper illustrates an incomplete sagittal septation of the bladder. The presence of a single opening between the labia and a common channel (urogenital sinus) draining both chambers and the elongated vagina indicates an arrest in normal development of the internal and external genitalia. This case underlines the importance of careful inspection of the newborn's genitalia. When an anomaly is found, early roentgenographic evaluation of the genitourinary system is essential to future medical or surgical management of these patients.

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LOCALIZED NODULAR SYNOVITIS OF THE KNEE: A REPORT OF TWO CASES WITH ABNORMAL ARTHROGRAMS*

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ABSTRACT:

The arthrographic appearance in two cases of localized PVS of the knee involving the region of the infrapatellar fat pad is reported. Lesions in this area may present with confusing symptomatology, and the true abnormality may be overlooked in a search for a meniscal lesion. The arthrographic picture is non-specific and a number of entities must be considered.

PIGMENTED villonodular synovitis (PVS) is a benign proliferative disease of synovial tissue which may be either diffuse or localized and nodular. Preoperative diagnosis by double contrast arthrography has been reported in the diffuse form of the disease,[9] but there are no reports using arthrography for diagnosis of the less common nodular form. Recently, we have seen two cases of nodular PVS of the knee with arthrographic abnormalities localized to the region of the infrapatellar fat pad. A paucity of material describing the normal arthrographic appearance of this region led to further investigation.

REPORT OF CASES

CASE I. A 25 year old man complained of a "popping" sensation in his right knee, present for five months, with intermittent locking. Clinical examination revealed audible and palpable clicking with flexion and with forceable extension in internal rotation. Arthrography showed normal menisci, but a prominence was noted in the region of the infrapatellar fat pad (Fig. 1*A*). Because of clinical findings, the lateral meniscus was removed, but the clicking persisted. Further intraoperative investigation showed a large fibrous mass, which appeared to arise from the infrapatellar fat pad which was then excised. On gross examination a firm, well-circumscribed mass measuring 2.5×2×2 cm was attached to adjacent adipose tissue (Fig. 1*B*). Histologic study revealed fibrous proliferation with many histiocytes, occasional foamy histiocytes, and multinucleated giant cells, many containing hemosiderin pigment (Fig. 1, *C* and *D*).

CASE II. A 15 year old girl complained of right knee pain and recurrent buckling following a bicycle accident one year prior to examination. The clinical interpretation was a torn medial meniscus, but an arthrogram revealed normal menisci. Retrospectively, a prominent intra-articular bulge in the region of the infrapatellar fat pad was present on the overhead lateral view (Fig. 2*A*). A few weeks later she twisted her knee which locked in 10° of flexion. At surgery, a large pedunculated mass measuring 4×2×1 cm extended into the intercondylar notch from the region of the infrapatellar fat pad. It was partially attached to the ligamentum mucosum. There was surrounding synovial inflammation. Histologic examination revealed many spindle shaped cells with formation of collagen fibers. Hemosiderin-laden macrophages with multinucleated giant cells and foamy histiocytes were present (Fig. 2*B*).

DISCUSSION

The first description of the entity now known as PVS is credited to Chassignac (1852) in a case report which he called cancer of the tendon sheath.[1] Jaffe *et al.*[5] introduced the term PVS in 1941, stressed the benign course of the disease, and raised

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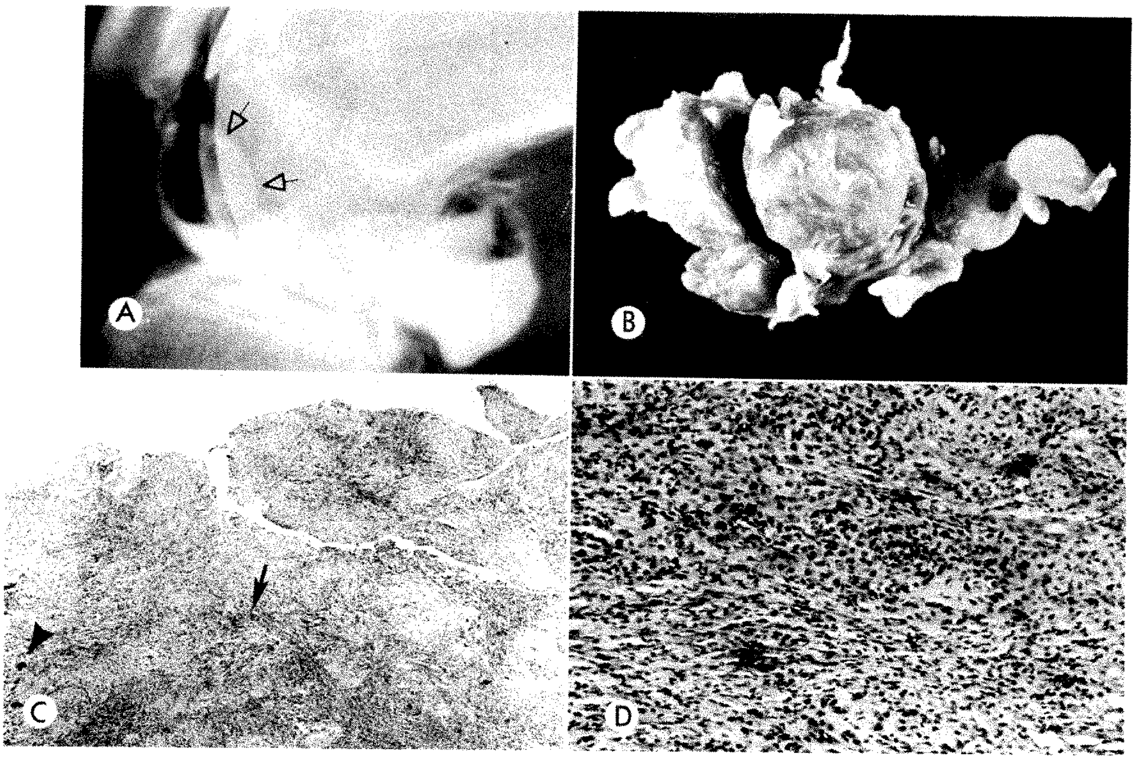

FIG. 1. Case 1. (*A*) On a lateral roentgenogram of the flexed knee following double-contrast arthrography, the nodular mass is clearly identifiable (arrows). (*B*) A photograph of the removed and sectioned specimen reveals a fibrous well-circumscribed mass. (*C*) A photomicrograph (×135) outlines fibrous proliferation with a villonodular pattern, pigmented cells (arrow), and occasional giant cells (arrowhead). (*D*) At a higher power of magnification (×540), round and spindle-shaped cells are present with scattered areas of pigmentation.

the possibility of an inflammatory etiology. Exclusive of hand lesions (giant-cell tumor of the tendon sheath), the knee is the most commonly involved joint, and many cases of diffuse involvement have been described. Reports of the localized nodular form in the knee have been less frequent. To our knowledge, arthrographic findings have not been reported in nodular PVS. In these two cases, the history suggested a mechanical derangement of the knee involving the menisci. Both patients experienced locking and no masses were palpable. In each case, at surgery a solitary mass was present, firmly attached to the synovium in the region of the infrapatellar fat pad. The lesions were excised and neither has recurred. Histologic evaluation revealed fibrous proliferation, a combination of histiocytes, multinucleated giant cells, and hemosiderin-laden macrophages, typical of localized nodular synovitis.

In diffuse PVS, the clinical setting usually includes a young adult with chronic knee pain, joint stiffness, synovial thickening, palpable masses, and serosanguineous effusion. The typical arthrographic appearance of the diffuse form is an enlarged joint cavity in association with irregular masses containing villous synovial projections.

Patients with localized nodular PVS in the knee usually lack the chronic inflammatory pattern of the diffuse form and most often present with symptoms suggesting a mechanical problem.[3] In the absence of a palpable mass, the diagnosis is elusive. Preoperative arthrography may be obtained. Arthrographic technique usually stresses careful, coned examination of the menisci, with less attention directed toward lesions in other parts of the joint. Thus, a localized mass, especially in sites other than

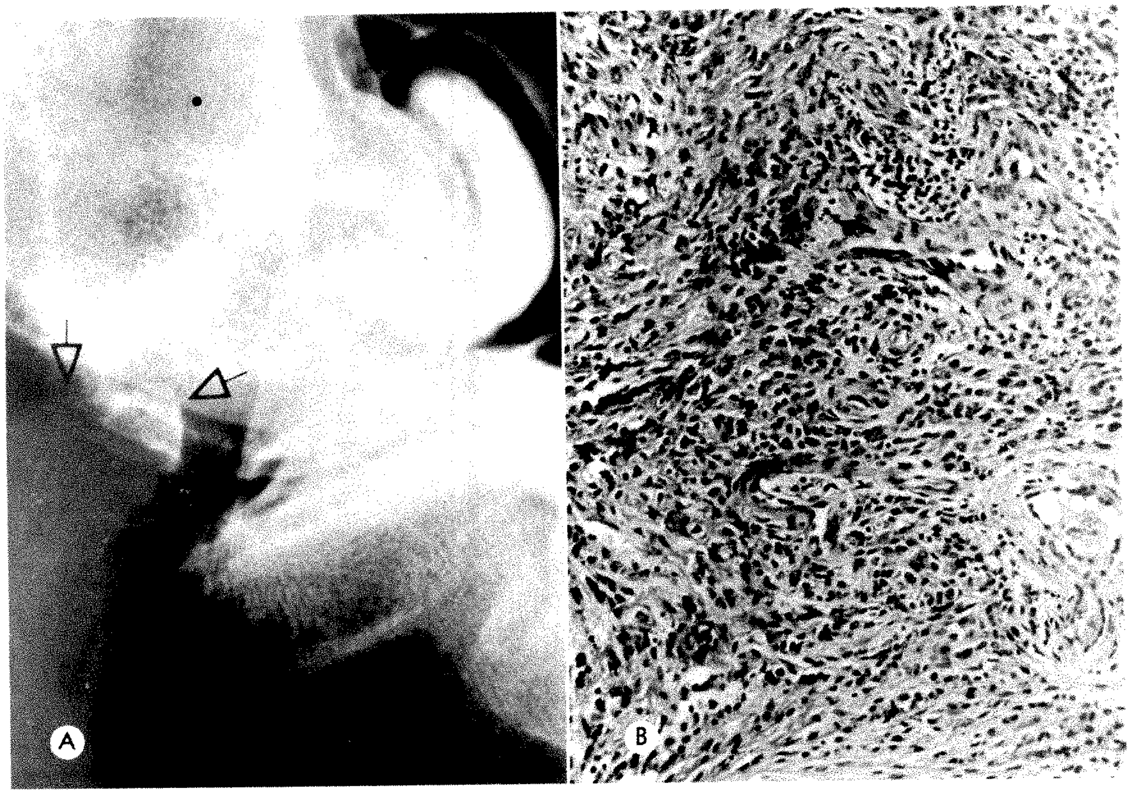

FIG. 2. Case II. On a lateral roentgenogram of the flexed knee following double-contrast arthrography, a well-circumscribed shadow (arrows) projects into the anterior aspect of the joint. (*B*) A photomicrograph (×540) outlines fibrous tissue admixed with round and spindle-shaped cells. Mildly pigmented cells are occasionally noted (arrow).

the suprapatellar bursa, may be overlooked. Although the nodular masses in localized PVS may be attached to the synovium at any site in the joint or even to a meniscus, our cases are unusual because the masses arose adjacent to the infrapatellar fat pad.

The infrapatellar fat pad is an extrasynovial intracapsular structure situated between the patellar tendon and femoral condyles (Fig. 3*A*). Synovium reflects over the fat pad, and a triangular fold, the ligamentum mucosum (alar fold), extends upward and posteriorly to attach in the intercondylar notch.

The normal arthrogram outlines a smooth synovial covering over the fat pad. It is usually concave but may rarely be straight or slightly convex in appearance, and is best evaluated on the slightly flexed lateral film (Fig. 3*B*). A small synovial recess may be present under the inferior portion of the fat pad.

Several entities may produce a localized mass or synovial irregularity in the region of the infrapatellar fat pad. Recurrent trauma and inflammation of the fat pad lead to formation of hypertrophic villi which may project into the joint.[7] Such damage has been noted in association with meniscal lesions and has also been described as a separate clinical entity, Hoffa's disease.[4] Tissue from a medial meniscus tear may displace the fat pad, producing a mass. Similar displacement may rarely result from an intra-articular ganglion arising from the alar fold of synovium.[6] Uncalcified intra-articular bodies may locate in the space over the fat pad between the femoral condyles.[8] Finally, other rare synovial tumors such as fibromas, hemangiomas,[2] or giant cell tumors[7] may produce localized arthrographic defects.

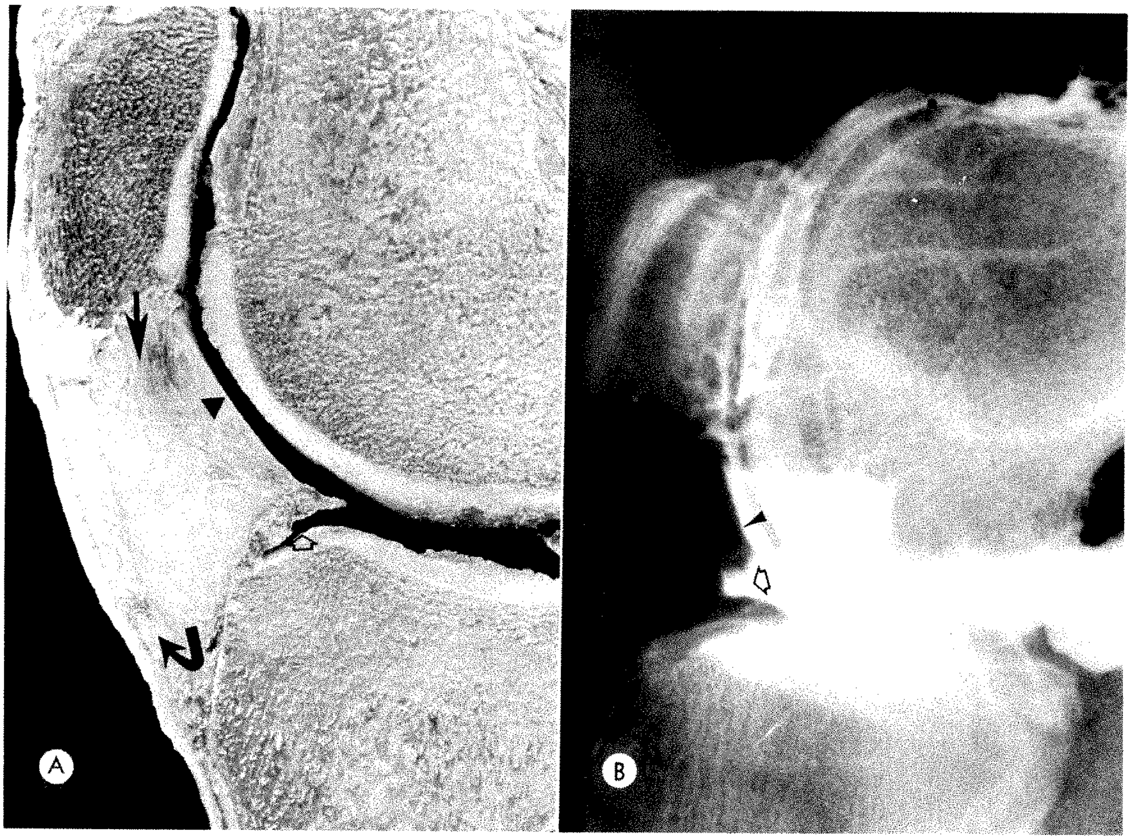

FIG. 3. Anatomy and normal arthrography. (*A*) A photograph of a sagittal section of a cadaveric knee demonstrates the infrapatellar fat pad (straight arrow) beneath the patellar tendon (curved arrow). Synovium is reflected over the fat pad (arrowhead) and a small recess is located beneath the fat pad (open arrow). (*B*) A lateral view of a normal double-contrast arthrogram reveals a smooth concave synovial covering over the fat pad (arrowhead) and a small inferior synovial recess (open arrow).

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ANNUAL MEETING: September 20–24, 1976, Washington, D. C., Washington Hilton Hotel.

SCIENTIFIC PROGRAM: Seymour Ochsner, *President Elect*, Ochsner Clinic, New Orleans, La.

MANAGER ANNUAL MEETING: George A. Kling, Harper Hospital, Detroit, Mich.

MEMBERSHIP: Hymer Friedell, Chairman, Executive Council,
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Representative on the Board of Chancellors of the American College of Radiology: J. A. del Regato.
Liaison Representative on the National Council on Radiation Protection and Measurements: Lawrence W. Davis.

ANNUAL MEETING: May 9–14, 1976, Vancouver, British Columbia, Bayshore Inn.

SCIENTIFIC PROGRAM: Felix N. Rutledge, *President*, Houston, Texas

LOCAL ARRANGEMENTS: John M. W. Gibson, Vancouver, British Columbia

MEMBERSHIP: Richard H. Jesse, *Secretary*, M. D. Anderson Hospital and Tumor Institute,
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EDITORIAL

GUIDELINES FOR THE MODERN CARDIAC CATHETERIZATION-ANGIOCARDIOGRAPHIC LABORATORY: REPORT OF THE INTER-SOCIETY COMMISSION FOR HEART DISEASE RESOURCES

THE modern cardiac catheterization-angiocardiographic laboratory is a complex organization. It requires a capital investment of $400,000 or more, 500 net square feet of prime radiologic space, a staff which includes at least two and usually four or more physicians, nurses, x-ray technologists, physiology technicians, and the backup needed for cine and large film processing. The laboratory is constantly confronted with patients at risk who require intravascular catheter procedures to attain physiologic and morphologic data on which to base the management of their problem.

As the pandemic of coronary surgery has spread throughout the nation, the demand for coronary arteriography—a procedure rarely even thought of a decade and a half ago—has burgeoned. There are probably 600–700 hospitals throughout the country in which sophisticated catheterization-angiocardiographic procedures are performed. In 1975, more than 200,000 coronary arteriograms were performed at a cost of about $350,000,000 if costs of hospitalization and laboratory procedures during the hospital stay are included. The procedures are not without risk: they have a defined mortality and morbidity. There is nothing more frustrating or dangerous than an incomplete or inadequate study. In the words of this report, such failures constitute "double jeopardy." That the quality of coronary arteriography around the nation is not uniformly high is indicated by the need felt in many centers to repeat a significant percentage of the coronary arteriograms on patients referred for cardiovascular surgery. All who have been exposed to the national experience are in agreement that the quality of coronary arteriography leaves a great deal to be desired.

Furthermore, there is no clear mandate that exclusively reserves coronary angiography to either the cardiologist or the radiologist. In some institutions, it is the total responsibility of the radiologist; in some, the cardiologist; and in many, they work in collaboration, with the cardiologist responsible for physiologic data retrieval and the radiologist for angiographic data retrieval. This last arrangement is ideal, and it is precisely this approach that the current report of the Inter-Society Commission for Heart Disease Resources delineates and supports.[1]

Five years ago, the first report of this committee appeared in *Circulation*.[2] It was a landmark effort to describe and to define the laboratory to which all hospitals might aspire. In fact, cardiologists, radiologists, hospital administrators, and public health authorities used the document as a major reference in their approach to the planning of new installations throughout the country. It was never the intent of the original committee that the report would not be subject to change: in point of fact, the capacity for systematic updating of the recommendations was implicit in the first report.

The new document not only reviews the optimal facilities for the catheterization–angiocardiographic laboratory but also the facilities for conventional x-ray examination of the heart and lungs and the radiologic capability of cardiovascular surgical operating rooms and intensive care units. In the authoritativeness of its recommendations as well as the detailed character of its treatment, it represents a major contribution to the quest for excellence in cardiovascular care. The physician will rely on it, and the hospital director and health planning agencies will use it as the standard against which to judge the certification of need for new and remodeled laboratories. Thus the report is required reading for all workers in the cardiovascular radiology field.

The report recommends the location of the catheterization laboratory "within or in close proximity to the hospital's primary radiologic facilities, adjacent to other radiographic laboratories." The rationale for this recommendation is based on optimal utilization of equipment, space, and personnel; on rapid response to equipment breakdown; and on the availability in radiology of precisely the kinds of supporting facilities which the laboratory requires to function effectively. The report describes in detail approaches to administration of the laboratory; the qualifications of the professional and nonprofessional staff; the levels of utilization which justify investment in so expensive and complex a unit; space requirements; equipment for physiologic studies; and the equipment that comprises the heart of the radiologic installation itself. Wherever possible, the recommendations are specific and the language precise. Recording methods such as large film, cine systems, and modern photofluorographic approaches are described and evaluated. Such essential elements as the video system, the film changers, the catheterization table, cine processing, film transport, image optics—all of these are dealt with trenchantly.

This report, then, constitutes an important and impressive contribution to the literature on cardiovascular radiologic facilities. The expert will find it extraordinarily well organized and inclusive. The novice will discover a bible to which he may return repetitively for scripture and verse and for a codification of the best thinking in the field.

The committee that produced this report was chaired by Melvin P. Judkins, and he has done an extraordinary job. In turn, it was the remarkable effort of Donald Fredrickson and Irving Wright who generated the earlier series of ICHD reports.[3] To all of the members of the committee we are indebted for a document which will be of enormous help to those involved in specialized cardiovascular procedures.

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NEWS ITEMS

RADIOLOGICAL PHYSICS AND RADIATION BIOLOGY

A refresher course of selected topics in the physics and radiation biology of diagnostic radiology will be offered in Dallas, Texas, May 17–20, 1976. Co-sponsors are the Radiology Department of Southwestern Medical School and the A. Webb-Roberts Center for Continuing Education of the University of Texas Health Science Center at Dallas.

The course is designed for residents preparing for board examinations and for radiologists seeking information on current knowledge and trends in the basic radiological sciences.

The course is acceptable for 26 hours credit under Category 1 for the American Medical Association Physician's Recognition Award.

The faculty will include, Donald E. Carlson, Ph.D., Edward E. Christensen, M.D., Thomas S. Curry III, M.D., Glenn V. Dalyrymple, M.D., J. Edward Dowdey, Ph.D., Mary Esther Gaulden, Ph.D., William R. Hendee, Ph.D., and Robert Murry, M.D.

For further information, please write to: Mary Esther Gaulden, Ph.D., Department of Radiology, Southwestern Medical School, 5323 Harry Hines Boulevard, Dallas, Texas 75235.

NUCLEAR RADIOLOGY

The New York University Post-Graduate Medical School, Department of Radiology, is offering a course on Nuclear Radiology, May 29–30, 1976, in New York City.

This course provides a comprehensive analysis of the current status of nuclear radiology. Time will be devoted to a review of related sciences although the main emphasis will be on practical clinical diagnosis. There will be a comprehensive review of imaging procedures in the various diagnostic categories and the most current clinical applications will be emphasized. These sessions are directed to both practitioners and trainees in nuclear medicine and radiology. There will be time for discussion and interaction with lecturers.

This Continuing Medical Education offering meets the criteria for 14 hours of credit in Category 1 for the Physician's Recognition Award of the American Medical Association.

For further information, please contact: NYU Post-Graduate Medical School, Office of the Recorder, Room 4-44N LHB, 550 First Avenue, New York City, New York 10016.

GENERAL DIAGNOSTIC RADIOLOGY

The New York University Post-Graduate Medical School will present a five day course in General Diagnostic Radiology, May 31–June 4, 1976, in New York City.

The course will include a survey of all sub-specialties of diagnostic radiology with a discussion of computerized tomography and its application to the trunk and to the head. This is designed as a refresher for the practicing radiologist and to help prepare candidates for the Boards in Radiology. There will be stress on basic concepts but some attention will be given to new developments in the fields in diagnostic radiology.

Radiologists from New York University Medical School, as well as a distinguished guest faculty, will participate.

This Continuing Medical Education offering meets the criteria for 30 hours of credit in Category 1 for the Physician's Recognition Award of the American Medical Association.

For further information, please contact: NYU Post-Graduate Medical School, Office of the Recorder, Room 4-44N LHB, 550 First Avenue, New York City, New York 10016.

PHYSICS OF RADIOLOGY, RADIOTHERAPY, NUCLEAR MEDICINE AND RADIOBIOLOGY

A refresher course on the Physics of Radiology, Radiotherapy, Nuclear Medicine and Radiobiology, will be held May 10–14, 1976, at the Queens Hospital Center, Jamaica, New York.

The program chairman is Gerald Shapiro, M.S., Chief Physicist, Department of Radiology.

An intensive review and refresher course will be presented on five consecutive afternoons for residents in radiology who are preparing for an examination by the American Board of Radiology. Emphasis will be placed on preparation for and the answering of Board questions. It is expected that all students will have had previous training in radiological physics.

This Continuing Medical Education offering meets the criteria for 20 hours of credit in Category I for the Physician's Recognition Award of the American Medical Association.

For further information, please contact: Jan J. Smulewicz, M.D., Director—Department of Radiology, Queens Hospital Center Affiliation, Long Island Jewish-Hillside Medical Center, 82-68 164th Street, Jamaica, New York 11432.

DIAGNOSIS AND TREATMENT OF BREAST DISEASES

A one day symposium on Diagnosis and Treatment of Breast Diseases will be held Friday, April 23, 1976 at the Queens Hospital Center, Jamaica, New York.

The program chairman is Jacob Dorfman, M.D., Attending Radiologist.

An intensive one day symposium will be presented on the clinical and radiological diagnosis and treatment of breast diseases. The conference will be open to both attending physicians and residents in all fields of medicine.

This Continuing Medical Education offering meets the criteria for 8 hours of credit in Category I for the Physician's Recognition Award of the American Medical Association.

For further information, please contact: Jan J. Smulewicz, M.D., Director—Department of Radiology, Queens Hospital Center Affiliation, Long Island Jewish-Hillside Medical Center 82-68 164th Street, Jamaica, New York, 11432.

BOOK REVIEW

Diagnostic Uses of Ultrasound. By Barry B. Goldberg, M.D., Head, Section of Diagnostic Ultrasound, Episcopal Hospital; Professor of Radiology, Temple University Health Sciences Center, Philadelphia, Pa.; Morris N. Kotler, M.D., Head, Non-Invasive Cardiac Laboratory, Hahnemann Hospital; Associate Professor of Medicine, Hahnemann Medical College, Philadelphia, Pa.; Marvin C. Ziskin, M.D., M.S., Bm.E., Associate Professor of Radiology and Medical Physics, Temple University Health Sciences Center, Philadelphia, Pa.; and Robert D. Waxman, B.A., Consultant in Ultrasound, Episcopal Hospital, Philadelphia, Pa. Cloth. Pp. 466, with many illustrations. Price, $30.00. Grune & Stratton, Inc., 111 Fifth Avenue, New York, N.Y. 10003, 1975.

This well written, authoritative, relatively complete volume fulfills a need.

Its first two chapters cover basic principles and instrumentation and were written by Marvin C. Ziskin, M.D., a physician with an excellent background in physics. The fundamentals of the physics of sound are described along with diagrammatic illustrations and present information adequate for understanding the use of the method. Similarly, a chapter on instrumentation describes thoroughly the basic components of the commonly used ultrasound systems. The principles of the three modes of echo display are well explained as is the physical background for the Doppler application of ultrasound.

Echocardiography, as a special field, is covered by Morris N. Kotler, M.D. Excellent illustrations of echograms of most of the described valvular lesions and of other cardiac abnormalities are presented. Determination of physiologic cardiac parameters and congenital heart anomalies is briefly described. The clinical and hemodynamic findings are included, as these are necessary in understanding the specific echograms.

The major portion of the book, six chapters covering the head and neck, chest, retroperitoneal structures, intraperitoneal structures, and gynecology and obstetrics, is written by the principal author, Barry B. Goldberg, M.D. Echoencephalographic techniques and measurements are described together with short discussions of thyroid and ophthalmologic applications. Examination of the kidneys is covered extensively and there are good representative sonograms. Examination of the liver, gallbladder, and spleen is well covered, but unfortunately ultrasonography of the pancreas is less extensively covered. A longer discussion of this subject, considering the importance of the ultrasonic diagnosis in pancreatic disease, would have been valuable. The final chapter deals with techniques of Doppler ultrasound.

As is true in most of the presently available textbooks covering ultrasound, the great majority of the illustrations presented are bistable sonograms instead of the ever more popular gray scale sonograms. Nevertheless, the book is well organized, easily read, and factual. It is an excellent textbook for students of ultrasound.

A. P. Zingas, M.D.

BOOKS RECEIVED

The Year Book of Cancer, 1975. Compiled and edited by Randolph Lee Clark, B.S., M.D., M.Sc. (Surgery), D.Sc. (Hon.), President, The University of Texas System Cancer Center; Professor of Surgery, The University of Texas M. D. Anderson Hospital and Tumor Institute; Member, President's Cancer Panel; Consultant, National Cancer Institute; F.A.C.S.; Russell W. Cumley, B.A., M.A., Ph.D., Editor and Head, Department of Publications, and Professor of Medical Journalism, The University of Texas System Cancer Center, M. D. Anderson Hospital and Tumor Institute; Executive Editor, The Medical Arts Publishing Foundation; with the editorial assistance of Joan E. McCay, B.A., M.A. Cloth. Pp. 655, with some illustrations. Price, $22.00. Year Book Medical Publishers, 35 E. Wacker Drive, Chicago, Ill. 60601, 1975.

Noninvasive Brain Imaging: Computed Tomography and Radionuclides. Edited by Harold J. DeBlanc, Jr., M.D., Director, Nuclear Medicine, University of Utah; and James A. Sorenson, Ph.D., Director, Medical Physics, University of Utah. Cloth. Pp. 220, with many illustrations. Price, $19.00. Published by the Society of Nuclear Medicine, Inc., 475 Park Avenue South, New York, N. Y. 10016. Distributed by Publishing Sciences Group, Inc., Acton, Mass., 1975.

Radiopharmaceuticals. Edited by Gopal Subramanian, Ph.D., Associate Professor, Division of Nuclear Medicine, Upstate Medical Center, Syracuse, N. Y.; Buck A. Rhodes, Ph.D., Director, Radiopharmacy Services; Professor of Diagnostic Radiology, and Pharmacy Practice, University of Kansas Medical Center, Kansas City, Kansas; James F. Cooper, Pharm.D., Head, Radiometrics Section; Assistant Professor of Medicinal Chemistry, University of Tennessee Medical Units, Memphis, Tenn.; and Vincent J. Sodd, Ph.D., Chief, Nuclear Medicine Laboratory, Bureau of Radiologic Health, FDA; Associate Professor, Department of Radiology, University of Cincinnati, Cincinnati, Ohio. Cloth. Pp. 555, with some illustrations. Price, $30.00. Published by the Society of Nuclear Medicine, Inc., 475 Park Avenue South, New York, N. Y. 10016, 1975.

Genital and Mammary Pathology Decennial, 1966–1975. Series Editor, Sheldon C. Sommers, M.D., Director of Laboratories, Lenox Hill Hospital, New York; Clinical Professor of Pathology, Columbia University College of Physicians and Surgeons, New York; Clinical Professor of Pathology, University of Southern California School of Medicine, Los Angeles, Calif. Cloth. Pp. 541, with many illustrations. Price, $22.75. Appleton-Century-Crofts, 292 Madison Ave., New York, N. Y. 10017, 1975.

An Atlas of Normal Roentgen Variants That May Simulate Disease. By Theodore E. Keats, M.D., Professor and Chairman, Department of Radiology, University of Virginia School of Medicine, Charlottesville, Va. Cloth. Pp. 351, with many illustrations. Price, $35.00. Year Book Medical Publishers, Inc., 35 E. Wacker Drive, Chicago, Ill. 60601, 1975.

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SOCIETY PROCEEDINGS

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Secretary, Dr. James Franklin Martin, 300 S. Hawthorne Rd., Winston-Salem, N. C. 27103. Annual Meeting: Washington Hilton, Washington, D. C., Sept. 20–24, 1976.

AMERICAN RADIUM SOCIETY
Secretary, Richard H. Jesse, Dept. of Surgery, M. D. Anderson Hosp. and Tumor Institute, Houston, Tex. 77025. Annual Meeting: Bayshore Inn, Vancouver, B. C., Canada, May 9–14, 1976.

RADIOLOGICAL SOCIETY OF NORTH AMERICA
Secretary, Dr. Theodore A. Tristan, Harrisburg, Pennsylvania. Annual Meeting:

AMERICAN COLLEGE OF RADIOLOGY
Executive Director, William C. Stronach, 20 N. Wacker Drive, Chicago, Ill. 60606. Annual meeting.

SECTION ON RADIOLOGY, AMERICAN MEDICAL ASSOCIATION
Secretary, Dr. Antolin Raventos, Davis, Calif. Annual Meeting.

AMERICAN BOARD OF RADIOLOGY
Secretary, Dr. C. Allen Good. Correspondence should be directed to Kahler East, Rochester, Minn. 55901.
Oral examinations will be held: Marriott Motor Hotel, Chicago, Ill., June 14–19, 1976; Sheraton Biltmore, Atlanta, Ga., Dec. 6–11, 1976.
Written examinations will be held in 14 selected sites on June 26, 1976.

Applications must be received in the Board Office before Sept. 30 of the year preceding the one in which the candidate wishes to be examined.

AMERICAN BOARD OF NUCLEAR MEDICINE, INC. A Conjoint Board of the American Boards of Internal Medicine, Pathology and Radiology and sponsored by the Society of Nuclear Medicine.

Application forms and further information are available from the American Board of Nuclear Medicine, 305 E. 45th St., New York, N. Y. 10017.

AMERICAN ASSOCIATION OF PHYSICISTS IN MEDICINE
Secretary, Dr. Robert G. Waggener, Dept. Radiol., Univ. Tex. Health Sciences Center, San Antonio, Tex. 78284 Annual Meeting:

AMERICAN SOCIETY OF THERAPEUTIC RADIOLOGISTS
Secretary, Dr. Robert W. Edland, 1836 South Ave., La Crosse, Wis., 54601. Annual Meeting:

AMERICAN NUCLEAR SOCIETY
Program Chairman, Werner K. Kern, IRD, Space Nuclear Systems, F 309, U. S. Atomic Energy Commission, Washington, D.C. 20545.

AMERICAN INSTITUTE OF ULTRASOUND IN MEDICINE
Secretary, John M. Reid, Ph.D., 556 18th Ave., Seattle, Wash. 98122. Annual Meeting.

AMERICAN SOCIETY OF NEURORADIOLOGY
Secretary, Arthur E. Rosenbaum, University of Pittsburgh, Pittsburgh, Pa. 15261. Annual Meeting: Peachtree Plaza Hotel, Atlanta, Ga., May 18–22, 1976.

FOURTEENTH INTERNATIONAL CONGRESS OF RADIOLOGY
Rio de Janeiro, Brazil, Oct. 23–29, 1977.
President Elect: Prof. Dr. Nicola C. Caminha; *General Secretary:* Dr. Durval Couto. Av. Churchill, 97-50 and-LC-39 20,000 Rio de Janeiro, Brazil.

INTERNATIONAL SOCIETY OF RADIOLOGY
Hon. Secretary-Treasurer, Prof. W. A. Fuchs, M.D., Department of Diagnostic Radiology, University Hospital, Inselspital, CH-3010 Bern, Switzerland.

TWELFTH INTER-AMERICAN CONGRESS OF RADIOLOGY
President, Dr. Publio Vargas Pazzos, Casilla 5227, Guayaquil, Ecuador. Meeting in Quito, Ecuador, 1979.

INTER-AMERICAN COLLEGE OF RADIOLOGY
President, Manuel Viamonte, Jr., M.D., Mt. Sinai Medical Center, 4300 Alton Rd., Miami Beach, Fla. 33140.
Secretary, Gaston Morillo, M.D., Jackson Memorial Hosp., 1700 N.W. 10th Ave., Miami, Fla. 33152.
Counselor for the United States, J. A. del Regato, M.D., Univ. of So. Fla. College of Medicine, 13000 No. 30th St., Tampa, Fla. 33612.

THIRD CONGRESS OF THE EUROPEAN ASSOCIATION OF RADIOLOGY
Secretary-General, P.O. Box 14, 79 Lauriston Place, Edinburgh BHI IDB, Scotland.

SECOND ASIAN AND OCEANIAN CONGRESS OF RADIOLOGY
Secretary, Dr. Buenaventura U. V. Angtuaco, Congress Secretariat Headquarters, 2161 Taft Ave., Manila, Philippines. Meeting:

ALABAMA CHAPTER OF ACR
Secretary-Treasurer, Dr. Lawrence E. Fetterman, 1720 Springhill Ave., Suite 201, Mobile, Ala. 36604. Meets time and place of Alabama State Medical Association.

ALASKA RADIOLOGICAL SOCIETY, CHAPTER OF ACR
Secretary-Treasurer, Dr. Maurice J. Coyle, 3200 Providence Ave., Anchorage, Alaska 99504.

AMERICAN OSTEOPATHIC COLLEGE OF RADIOLOGY
Annual Scientific Meeting: Americana Hotel, Bar Harbor, Fla. Program Administrator: Lawrence J. Jordan, D.O., Suite 21, Ponce American Bldg., 4601 Ponce de Leon Blvd., Coral Gables, Fla. 33146.

AMERICAN THERMOGRAPHIC SOCIETY
Secretary-Treasurer, John Wallace, Ph.D., Dept. Radiol., Thomas Jefferson Univ. Hosp., Philadelphia, Pa. 19107. Annual Meeting.

ARIZONA RADIOLOGICAL SOCIETY, CHAPTER OF ACR
Secretary, Dr. Irwin M. Freundlich, 1501 N. Campbell Ave., Dept. Radiol., Tucson, 85724. Two regular meetings a year. Annual meeting at time and place of State Medical Association and interim meeting six months later.

ARK-LA-TEX RADIOLOGICAL SOCIETY
Secretary, Dr. Erich K. Lang, 1541 Kings Highway, Shreveport, La. 71130. Meets monthly on fourth Wednesday, 8:00 P.M., Sept. to May.

ARKANSAS CHAPTER OF ACR
Secretary-Treasurer, Dr. Richard Seibold, Jr., Wadley Hosp., Texarkana, Ark.—Tex. 75501. Meets twice annually, the Spring Meeting being in conjunction with and at the place of the State Medical Association.

ASSOCIATION OF UNIVERSITY RADIOLOGISTS
Secretary-Treasurer, Dr. Arch W. Templeton, Univ. of Kansas Med. Center, 39th and Rainbow Blvd., Kansas City, Kansas 66103. Annual Meeting.

ATLANTA RADIOLOGICAL SOCIETY
Secretary-Treasurer, Dr. James H. Larose, Dept. Nuclear Med., South Fulton Hosp., East Point, Ga. 30344. Meets on four Thursday evenings during the academic year at a time announced in early September of each year, at various Atlanta restaurants.

*** Secretaries of societies are requested to send timely information promptly to the Editor.**

Bavarian-American Radiologic Society

Secretary, LTC. Marco J. DiBiase, M.D., Radiology Service, Heidelberg, 130 Station Hosp., APO N. Y. 09102. Meets quarterly.

Blockley Radiological Society

Secretary-Treasurer, Dr William H. Green, 616 East 24th St., Chester, Pa. 19013.

Bluegrass Radiological Society

Secretary-Treasurer, Dr. Eugene Slusher, Lexington Clinic, 1221 S. Broadway, Lexington, Ky. 40504. The Society meets once each month during the school year.

Bronx Radiological Society, New York State, Chapter ACR

Secretary-Treasurer, Dr. Leon J. Corbin, 1369 Rosendale Ave., Bronx, N. Y. 10472. Meets 4 times a year.

Brooklyn Radiological Society

Secretary-Treasurer, Dr. Ralph Brancaccio, 7901 4th Ave., Brooklyn, N. Y. 11209. Meets first Thursday of each month, October through June.

Buffalo Radiological Society

Secretary, Dr. George J. Alker, Jr., E. J. Meyer Mem. Hosp., Buffalo, N. Y. 14215. Meets second Monday evening each month, October to May inclusive, at University Club.

California Radiation Therapy Association

Secretary-Treasurer, Dr. Duane J. Gillum, Stanford Medical Center, Stanford, Calif. 94304. Meets semiannually in San Francisco and Los Angeles.

California Radiological Society, California Chapter of ACR

Secretary-Treasurer, Dr. John L. Gwinn, 4650 Sunset Blvd., Los Angeles, Calif. 90027.

Catawba Valley Radiological Society

Secretary, Dr. Walter Joe Jacumin, P.O. Box 265, Rutherford College, N. C. 28671. Meets the last Thursday of every month, Holiday Inn, Morganton, N. C. at 7:30 P.M.

Central New York Radiological Society

Secretary-Treasurer, Dr. Alfred Brettner, Auburn Mem. Hosp., Auburn, N. Y. 13021. Meets first Monday each month October through May.

Central Ohio Radiological Society

Secretary-Treasurer, Dr. Daniel E. Lewis, 309 East State St., Columbus, Ohio 43215. Meets second Thursday in October, November, January, March, and May at Fort Hayes Hotel, Columbus, Ohio.

Central Texas Radiology Society

Secretary-Treasurer Dr. E. Jerome Schoolar, Scott and White Clinic, Temple, Tex. 76501. Meets the fourth Monday of each month at Ponderosa Hotel, Temple, Tex. at 7:00 P.M.

Chicago Radiological Society, Division of the Illinois Radiological Society, Chapter of ACR

Secretary-Treasurer, Dr. Harold J. Lasky, 55 E. Washington St., Suite 1735, Chicago, Ill. 60602. Meets third Thursday of each month, October to April, except December, at the Bismark Hotel, Chicago, Ill.

Cleveland Radiological Society

Secretary-Treasurer, Dr. Charles M. Greenwald, 7007 Powers Blvd., X-Ray Dept., Parma, Ohio 44129. Meetings at 7:00 P.M. on fourth Monday of October, November, January, February, March and fifth Monday of April.

Colorado Radiological Society, Chapter of ACR

Secretary, Dr. John Pettigrew, Denver, Colo. Meets third Friday of each month at Denver Athletic Club from September through May.

Connecticut Valley Radiologic Society

Secretary, Dr. Gerald N. LaPierre, 759 Chestnut St., Springfield, Mass. 01107. Meets in April and October.

Dallas-Fort Worth Radiological Society

Secretary-Treasurer, Dr. Robert R. Burns, 1400 Stemmons Ave., Dallas, Tex. 75208. Meets the 3rd Monday of every month at 6:30 P.M., at the Airport Hotel, Arlington, Tex.

Delaware Chapter of ACR

Secretary, Dr. Ekkehard S. Schubert, Wilmington Med. Center, P. O. Box 1951, Wilmington, Del. 19899.

East Bay Radiological Society

Secretary-Treasurer, Dr. Richard H. Culhane, 4 Vista del Mar, Orinda, Calif. 74563. Meets first Thursday each month, Oct. through May, at University Club, Oakland, Calif.

East Tennessee Radiological Society

Secretary-Treasurer, Dr. George H. Wood, 205 Medical Arts Bldg., Knoxville, Tenn. 37902. Meets in January and September.

Florida Radiological Society, Chapter of ACR

Secretary. Dr. Paul J. Popovich, 1350 S. Hickory St., Melbourne, Fla. 32901. Meets twice annually, in the spring with the Annual State Society Meeting and in the fall.

Florida West Coast Radiological Society

Secretary-Treasurer, Dr. Herbert Johnson, Davis Blvd., Tampa, Fla. 33606. Meets on 4th Thursday of the months January, March, May, October, and November.

Georgia Radiological Society, Chapter of ACR

Secretary, Dr. E. P. Rasmussen, Piedmont Prof. Bldg., 35 Collier Rd., N.W., Atlanta, Ga. 30309.

Greater Cincinnati Radiological Society

Secretary-Treasurer, Dr. Owen L. Brown, 2421 Auburn Ave., Cincinnati, Ohio 45219.

Greater Kansas City Radiological Society

President-Secretary, Dr. Jay I. Rozen, Suite 216, 6400 Prospect, Kansas City, Mo. 64132. Meets 5 times a year.

Greater Louisville Radiological Society

Secretary-Treasurer, Dr. L. D. LeNeave, 315 E. Broadway, Louisville, Ky. 40202. Meets monthly.

Greater Miami Radiological Society

Secretary, Dr. David C. Hillman, P. O. Box 610544, North Miami, Fla. 33161. Meets monthly, third Wednesday at 8:00 P.M. at various member hospitals, Miami, Fla.

Greater St. Louis Society of Radiologists

Secretary-Treasurer, Dr. Donald Callahan, Northland Med. Bldg., Jennings, Mo. 63136.

Hawaii Radiological Society, Chapter of ACR

Secretary-Treasurer, Dr. Michael J. McCabe, Straub Clinic and Hosp., Honolulu, Hawaii 96813. Meets third Monday of each month at 7:00 P.M.

Health Physics Society

Secretary, Russell F. Cowing, P.O. Box 156, E. Weymouth, Mass. 02189. Annual Meeting.

Houston Radiological Society

Secretary, Dr. Neill B. Longley, 6436 Fannin, Suite 601, Houston, Tex. 77025. Meets fourth Monday of each month, except June, July, August and December, at 6:00 P.M., at 103 Jesse H. Jones Library Building, Texas Medical Center, Houston, Tex. 77025.

Idaho State Radiological Society, Chapter of ACR

Secretary-Treasurer, Dr. John H. Truksa, 1605 Park Ave., Nampa, Id. 83651. Meets in the spring and fall.

Illinois Radiological Society, Inc., Chapter of ACR

Secretary, Dr. Robert D. Dooley, Hinsdale Med. Center, Hinsdale, Ill. 60521. Meets in the spring and fall.

Indiana Roentgen Society, Inc., Chapter of ACR

Secretary, Dr. John A. Knote, Home Hosp., Lafayette, Ind. 47902.

Iowa Radiological Society, Chapter of ACR

Secretary-Treasurer, Dr. Dale L. Roberson, 1948 First Ave., NE, Cedar Rapids, Iowa 52402. Luncheon and business meeting during annual session of Iowa State Medical Society. The scientific session is held in the autumn.

Kansas Radiological Society, Chapter of ACR

Secretary-Treasurer, Dr. Ralph H. Baehr, 310 Medical Arts Bldg., Topeka, Kan. 66604. Meets in spring with State Medical Society and in winter on call.

Kentucky Chapter of ACR

Secretary-Treasurer, Dr. Bernard Sams, St. Joseph In-

firmary, 735 Eastern Parkway, Louisvlle, Ky. 40217. Meets in April and September.

Kings County Radiological Society
Secretary, Dr. Sidney Hendler, 1880 Ocean Ave., Brooklyn 30, N. Y. Meets Kings County Med. Soc. Bldg. monthly on fourth Thursday, October to May, 8:45 P.M.

Knoxville Radiological Society
Secretary, Dr. Clifford L. Walton, Blount Professional Bldg., Knoxville 20, Tenn. Meetings are held the third Monday of every other month at the University of Tennessee Memorial Research Center and Hospital.

Long Island Radiological Society
Secretary, Dr. Harry L. Stein, North Shore Univ. Hosp., 300 Community Dr., Manhasset, N. Y. 11030.

Los Angeles Radiological Society
Secretary, Dr. Arthur F. Schanche, 333 North Prairie Ave., Inglewood, Calif. 90301. Meets second Wednesday of month in September, November, January, April and June at Los Angeles County Medical Association Building, Los Angeles, Calif. Midwinter Radiological Conference. Century Plaza Hotel, Los Angeles, Calif.

Louisiana Radiological Society, Chapter of ACR
Secretary-Treasurer, Dr. Roger H. Tutton, 1514 Jefferson Hwy., New Orleans, La. 70121.

Louisiana-Texas Gulf Coast Radiological Society
Secretary-Treasurer, Dr. J. Gardiner Bourque, 3155 Stagg Dr., Suite 230, Doctors Bldg., Beaumont, Texas 77701.

Maine Radiological Society, Chapter of ACR
Secretary-Treasurer, Dr. Peter E. Giustra, Dept. Radiology, Penobscot Bay Medical Center, Rockland, Maine 04841. Meets in June, September, December and April.

Maryland Radiological Society, Chapter of ACR
Secretary, Dr. David S. O'Brien, Anne Arundel Hosp., Annapolis, Md. 21401.

Massachusetts Radiological Society, Chapter of ACR
Secretary, Dr. Joseph T. Ferrucci, Jr., Massachusetts Gen. Hosp., Boston, Mass. 02114.

Memphis Roentgen Society
Secretary-Treasurer, Dr. R. Randolph Ramey, Baptist Memorial Hosp., 899 Madison Ave., Memphis, Tenn. 38146. Meets first Monday Oct. through June at the University Club.

Miami Valley Radiological Society
Secretary, Dr. Bert Must, I.B.M. Bldg., Dayton, Ohio. Meets third Thursday of fall, winter and spring months at 7:30 P.M. at Miami Valley Hospital, Dayton, Ohio.

Michigan Radiological Society, Chapter of ACR
Secretary-Treasurer, Dr. Francis P. Shea, Harper Hospital, 3825 Brush St., Detroit, Mich. 48201. Meets monthly, first Thursday, October through May, at David Whitney House, 1010 Antietam, at 6:30 P.M.

Michigan Society of Therapeutic Radiologists
Secretary-Treasurer, Dr. William I. Knapp, St. Mary's Hosp., 830 S. Jefferson, Saginaw, Mich. 48601. Meets bimonthly during the academic year.

Mid-Hudson Radiological Society
Secretary-Treasurer, Dr. William D. Stiehm, 37 Flower Hill Rd., Poughkeepsie, N. Y. 12603. Meets 7:00 P.M., first Wednesday of each month, September to May.

Milwaukee Roentgen Ray Society
Secretary-Treasurer, Dr. Thomas C. Lipscomb, 1004 North Tenth St., Milwaukee, Wis. 53233. Meets monthly on fourth Monday, October through May, at University Club.

Minnesota Radiological Society, Chapter of ACR
Secretary-Treasurer, Dr. Marvin E. Goldberg, Box 292, Mayo Memorial Health Sciences Center, Minneapolis, Minn. 55455.

Mississippi State Radiological Society, Chapter of ACR
Secretary-Treasurer, Dr. Edward L. Gieger, 969 Lakeland Dr., Jackson, Miss. 39216. Meets third Thursday, excluding summer months, at the Primos Northgate Rest., Jackson at 6:30 P.M.

Missouri Radiological Society, Chapter of ACR
Secretary-Treasurer, Dr. Ronald G. Evens, Mallinckrodt Institute of Radiology, 510 S. Kingshighway, St. Louis, Mo. 63110.

Montana Radiological Society, Chapter of ACR
Secretary, Dr. C. H. Agnew, Room 102, Doctors Bldg., Billings, Mont. 59101.

Nebraska Chapter of ACR
Secretary-Treasurer, Dr. Robert Bodmer, Suite 622 Doctors Bdg., Omaha, Neb. 68131. Meets the third Wednesday of the month, Oct. through March, at the Clarkson Hosp., Omaha, Neb. and the fourth Friday of April at the Lincoln Country Club, Lincoln, Neb.

Nevada Radiological Society, Chapter of ACR
Secretary, Dr. Charles F. Veverka, Carson Tahoe Hosp., Carson City, Nev. 89701.

N.E. Society for Radiation Oncology
Secretary, Dr. C. C. Wang, Mass. Gen. Hosp., Boston, Mass. 02114.

New England Roentgen Ray Society
Secretary, Dr. Melvin E. Clouse, 185 Pilgrim Rd., Boston, Mass. 02115. Meets the third Friday of Oct. and Nov., and third Thurs. of each month. Jan. through May, excluding December, at The Longwood Towers, 20 Chapel Street, Brookline, Mass. at 3:00 P.M. Annual Meeting: May 20, 1976.

New Hampshire Roentgen Ray Society, Chapter of ACR
Secretary-Treasurer, Dr. Edward P. Kane, Claremont Gen. Hosp., Claremont, N. H. 03743. Meets four to six times yearly.

New Mexico Society of Radiologists, Chapter of ACR
Secretary, Dr. W. M. Jordan, 1100 Central Ave. S.E., Albuquerque, N. M. 87106. Four meetings annually, three held in Albuquerque, N. M., and one held at time and place of New Mexico State Medical Society annual meeting.

New Orleans Radiological Society, Inc.
Secretary-Treasurer, Dr. Jimmy L. Mains, P.O. Box 446, Gretna, La. 70053. Meets bimonthly at local restaurants selected by the President. Spring Conference.

New York Roentgen Society
Secretary-Treasurer, Dr. Thomas C. Beneventano, 111 East 210th St., Bronx, N. Y. 10467. Meets monthly on the 3rd Monday at the New York Academy of Medicine at 4:30 P.M. Annual Spring Conference, Waldorf-Astoria Hotel, New York, N. Y., April 22–24, 1976. A.M.A. Cat. I credit. Further information may be obtained from Dr. Albert A. Dunn, Roosevelt Hosp., New York, N. Y. 10019.

New York State Chapter of ACR
Secretary-Treasurer, Dr. Albert F. Keegan, 6 Secor Dr., Port Wash., N. Y. 11050.

North American Society of Cardiac Radiology
Secretary-Treasurer, Dr. Erik Carlson, Univ. Calif., San Francisco, Calif. 94143.

North Carolina Chapter of ACR
Secretary-Treasurer, Dr. Ernest B. Spangler, Wesley Long Hosp., Greensboro, N. C. 27402. Meets twice a year. The Spring Meeting is held at the time of the meeting of the North Carolina Medical Society. The Fall Meeting is held in November at the Mid Pines Club, Southern Pines, N. C.

North Dakota Radiological Society, Chapter of ACR
Secretary, Dr. Marshall Landa, P. O. Box 6001, Fargo, N. D. 58102. Meets at time of State Medical Association meeting. Other meetings arranged on call of the President.

North Florida Radiological Society
Secretary, Dr. David F. Bew, University Hospital of

Jacksonville, 655 W. Eighth Street, P.O. Box 2751, Jacksonville, Fla. 32203. Meets quarterly in March, June, September and December.

Northeastern Oklahoma Radiological Society
Secretary-Treasurer, Dr. Theodore J. Brickner, Jr., 5919 S. Gary Place, Tulsa, Okla. 74110.

Northeastern New York Radiological Society
Secretary, Dr. Donald R. Morton, Dept. of Radiology, St. Clare's Hosp., Schenectady, N. Y. 12304. Meets in Albany area on third Wednesday of October, November, March, April, and May.

Northern California Radiation Therapy Association
Secretary-Treasurer, Dr. John D. Earle, Stanford Medical Center, Stanford, Calif. 94304. Meets quarterly.

Northern California Radiological Society
Secretary, Dr. Patrick J. Grinsell, 1207 Fairchild Ct., Woodland, Calif. 95695. Meets on the fourth Monday, Sept. through May at the Mansion Inn, Sacramento, Calif.

Northwestern New York Radiological Society
Secretary, Dr. Barbara E. Chick, Glens Falls Hospital, Glens Falls, N. Y. 12801.

Northwestern Ohio Radiological Society
Secretary, Dr. Richard W. Siders, 421 Michigan, Toledo, Ohio 43624. Meets 3rd Wednesday from September to May.

Ohio State Radiological Society, Chapter of ACR
Secretary, Dr. James Farmer, Cleveland, Ohio.

Oklahoma State Radiological Society, Chapter of ACR
Secretary, Dr. George H. Ladd, 4616 Denison, Muskogee, Okla. 74401. Meets in January, May and October.

Orange County Radiological Society
Secretary, Dr. William E. Danko, 2601 E. Chapman, Orange, Calif. 92667. Meets on fourth Tuesday of the month, excluding June, July, August, and December, at Orange County Medical Association Bldg., Orange, Calif.

Oregon State Radiological Society, Chapter of ACR
Secretary-Treasurer, Dr. Ray F. Friedman, 3324 S. W. 44th St., Portland, Ore. 97221. Meets on second Wednesday of month, October through April, at the University Club, Portland, Ore.

Orleans Parish Radiological Society
Secretary, Dr. Joseph V. Schlosser, Charity Hospital, New Orleans, La. 70113. Meets second Tuesday of each month.

Pacific Northwest Radiological Society
Secretary-Treasurer, Dr. Kenneth D. Moores, 1118 9th Ave., Seattle, Wash. 98101. Annual Meeting: Benson Hotel, Portland, Ore., May 7–9, 1976.

Pennsylvania Radiological Society, Chapter of ACR
Secretary, Dr. Joseph A. Marasco, Jr., St. Francis General Hosp., Pittsburgh, Pa. 19141.

Philadelphia Roentgen Ray Society
Secretary, Dr. Marvin E. Haskin, 230 N. Broad St., Philadelphia, Pa. 19102. Meets first Thursday of each month at 5 P.M., from October to May in Thompson Hall, College of Physicians.

Pittsburgh Roentgen Society
Secretary, Dr. Klaus M. Bron, Presbyterian-Univ. Hosp., Pittsburgh 15213. Meets second Wednesday of month, September through May, at the Pittsburgh Athletic Association.

Radiation Research Society
Executive Secretary, Richard J. Burk, Jr., 4211 39th St., N.W., Washington, D. C. 20016. Annual Meeting.

Radiological Society of Connecticut, Inc., Chapter of ACR
Secretary, Dr. Gerald L. Baker, 85 Jefferson St., Hartford, Conn. 06106. Meets in Oct., Jan., March, and June.

Radiological Society of Greater Cincinnati
Secretary-Treasurer, Dr. Alvin Nathan, c/o Academy of Medicine, 320 Broadway, Cincinnati, Ohio 45202. Meets first Monday of each month at Cincinnati Academy of Medicine.

Radiological Society of New Jersey, Chapter of ACR
Secretary, Dr. Fred M. Palace, 11 Dale Dr., Morristown, N.J. 07960. Monthly meetings in East Orange and Trenton, N.J. Semi-Annual Meeting in Nov.

Radiological Society of Rhode Island, Chapter of ACR
Secretary-Treasurer, Dr. Daniel J. Alves, Rhode Island Hosp., Providence, R. I. 02902.

Radiological Society of Southern California
Secretary-Treasurer, Dr. A. Franklin Turner, LAC-USC Medical Center, Room 3418, 1200 North State St., Los Angeles, Calif. 90033. Meets three times a year, usually October, February and May.

Radiological Society of the State of New York
Secretary-Treasurer, Dr. John W. Colgan, 273 Hollywood Ave., Rochester, N. Y. 14618.

Redwood Empire Radiological Society
Secretary, Dr. Charles E. Carter, 121 Sotoyome St., Santa Rosa, Calif. 95405. Meets second Monday every other month.

Richmond County Radiological Society
Secretary, Dr. Frederick S. Vines, 11830 Rothbury Dr., Richmond, Va. 23235. Meets third Thursday of each month at the Aberdeen Barn.

Rochester Roentgen Ray Society, Rochester, N. Y.
Secretary-Treasurer, Dr. Robert J. Bruneau, Rochester General Hosp., Rochester, N. Y. 14621. Quarterly meetings on the call of the President, at the Rochester Academy of Medicine.

Rocky Mountain Radiological Society
Secretary-Treasurer, Dr. Lorenz R. Wurtzebach, 4200 E. Ninth Ave., Denver, Colo. 80220. Annual Meeting: Brown Palace Hotel, Denver, Colo., Aug. 19–21, 1976.

San Antonio-Civilian Military Radiological Society
Secretary, Dr. James R. Stewart, Oak Hills Medical Ctr., San Antonio, Tex. 78209. Meets third Wednesday of each month at Fort Sam Houston Officers Club at 6:30 P.M.

San Diego Radiological Society
President, Dr. Donald J. Fleischli, 7849 Fay Ave., La Jolla, Calif. 92037. Meets the first Wednesday of each month Sept. through June at the University Club.

San Francisco Radiological Society
Secretary-Treasurer, Dr. Robert L. Koch, 3838 California St., Suite 106, San Francisco, Calif. 94118.

Section on Radiology, California Medical Association
Secretary, Dr. William H. Graham, 630 East Santa Clara St., San Jose, Calif.

Section on Radiology, Medical Society of the District of Columbia
Secretary-Treasurer, Dr. Albert M. Zelna, 21 Masters St., Potomac, Md. 20854. Meets at Medical Society Library, third Wednesday of January, March, May and October at 8:00 P.M.

Section of Radiology, National Medical Association
Secretary, Dr. Ruby Brooks, Dept. Radiol., Veterans Adm. Hosp., P.O. Box 511, Tuskogee, Ala. 36083. Annual Meeting.

Section on Radiology, Southern Medical Association
Secretary, Dr. Mario A. Calonje, 1514 Jefferson Highway, New Orleans, La. 70121. Annual Meeting.

Section on Radiology, Texas Medical Association
Secretary, Dr. George F. Crawford, St. Elizabeth Hospital, Beaumont, Tex. Meets annually with the Texas Medical Association.

Society for Pediatric Radiology
Secretary-Treasurer, Dr. John P. Dorst, 601 N. Broadway, Baltimore, Md. 21205. Annual meeting: Washington Hilton Hotel, Washington, D.C., Sept., 19, 1976.

Society of Gastro-intestinal Radiologists
Secretary-Treasurer, Dr. John R. Amberg, University Hospital, 225 W. Dickinson St., San Diego, Calif. 92103.

Society of Nuclear Medicine

Secretary, Dr. E. James Potchen, Edward Mallinckrodt Institute of Radiology, 660 S. Euclid Ave., St. Louis, Mo. 63110. *Administrative Officer*, Mrs. Margaret Glos, 211 E. 43rd St., New York, N. Y. 10017. Annual Meeting.

South Bay Radiological Society

Secretary, Dr. Robert Mindalzun, Valley Radiologists, Inc., 100 O'Connor Dr., San Jose, Calif. 95128. Meets the 2nd Monday of each month at the Santa Clara County Medical Society Bldg., 700 Empey Way, San Jose, Calif.

South Carolina Radiological Society, Chapter of ACR

Secretary, Dr. George W. Brunson, 1406 Gregg St Columbia, S. C. Annual meeting (primarily business) in conjunction with the South Carolina Medical Association meeting in May. Annual fall scientific meeting at time and place designated by the president.

South Coast Radiological Society Chapter of ACR

Secretary-Treasurer, Dr. Richard T. Love, Santa Barbara Med. Clin., 215 Pesetas Lane, Santa Barbara, Calif. 93110. Meets fourth Tuesday of alternate months, Sept., Nov., Jan., March and May.

South Dakota Radiological Society, Chapter of ACR

Secretary, Dr. M. F. Petereit, 2416 S. Phillips, Sioux Falls, S. D. 57105. Meets in spring with State Medical Society and in fall.

Southern California Radiation Therapy Association

Secretary-Treasurer, Dr. Duane J. Gillum, 250 W. Pueblo St., Santa Barbara, Calif. 93105. Meets quarterly.

Southern Radiological Conference

Secretary-Treasurer, Dr. J. W. Maxwell, P.O. Box 2144 Mobile Ala. 36601. Annual Meeting:

Tennessee Radiological Society, Chapter of ACR

Secretary-Treasurer, Dr. Jerry W. Grise, Methodist Hosp., 1265 Union Ave., Memphis, Tenn. 38104. Meets annually at the time and place of the Tennessee State Medical Association meeting.

Texas State Radiological Society, Chapter of ACR

Secretary, Dr. Francis E. O'Neill, 1128 Nix Prof. Bdg., San Antonio, Tex. 78205.

The Fleischner Society

Secretary, Dr. E. Robert Heitzman, State University of New York Upstate Medical Center, Syracuse, N. Y. 13210. Annual Meeting:

Tri-State Radiological Society

Secretary, Dr. Thomas Harmon, St. Mary's Hosp., Evansville, Ind. 47750. Meets bimonthly on the third Wednesday at area Hospitals.

Upper Peninsula Radiological Society

Secretary, Dr. A. Gonty, Menominee, Mich. Meets quarterly.

Utah State Radiological Society, Chapter of ACR

Secretary-Treasurer, D. Michael Edson, Dept. Radiol., Valley West Hosp., 4160 West 3400 South, Granger, Utah 84120. Meets quarterly at Holy Cross Hospital.

Vermont Radiological Society, Chapter of ACR

Secretary, Dr. J. Lorimer Holm, R.R. #3, Barre, Vt. 05641.

Virginia Chapter of ACR

Secretary-Treasurer, Dr. Charles P. Winkler, 3500 Kensington Ave., Suite 2-A, Richmond, Va. 23221.

Washington, D. C., Chapter of ACR

Secretary-Treasurer, Dr. Robert M. Allen, 9312 Convento Terr., Fairfax, Va. 22030.

Washington State Radiological Society, Chapter of ACR

Secretary-Treasurer, Dr. Donald J. Hesch, 3216 N.E. 45th Place, Seattle, Wash. 98105.

West Virginia Radiological Society, Chapter of ACR

Secretary-Treasurer, Dr. Andrew W. Goodwin, II, 200 Med. Arts Bldg., Charleston, W. Va. 25301. Meets concurrently with annual meeting of West Virginia State Medical Society, other meetings arranged by program committee.

Westchester County Radiological Society

Secretary, Dr. Leonard Cutler, 16 Guion Place, New Rochelle, N. Y. 10802. Meets on second Tuesday of October, December, February and May.

Wisconsin Radiological Society, Chapter of ACR

Secretary-Treasurer, Dr. June Unger, Wood VA Hosp., Wood, Wis. 53193. Meets twice a year, May and September.

Wisconsin Society of Therapeutic Radiologists

Secretary, Dr. Alvin Greenberg, Radiother. Ctr., Univ. Hospitals, Madison, Wis. 53706. Meets quarterly.

Wyoming Radiological Society, Chapter of ACR

Secretary, Dr. Ross J. Collie, Box 96, Lander, Wyo. 82520. Meets in fall with State Medical Society and in spring on call of President.

MEXICO, PUERTO RICO AND CENTRAL AMERICA

Asociación Costarricense de Radiología

Secretary, Dr. Rafael Umaña-Umaña, Apartado 8-5340, San José, Costa Rica.

Asociacón de Radiólogos de Centro America y Panamá. Comprising: Guatemala, El Salvador, Honduras, Nicaragua, Costa Rica and Panamá

Secretary-General, Dr. Francisco Miranbell Solis, Apartado 3352, San José, Costa Rica, Central America. Meets annually in a rotating manner in the six countries.

Sociedad de Radiología de Salvador

Secretary, Dr. Carlos Meijia, 5a Av. Nte. No. 434, San Salvador, Rep. El Salvador.

Sociedad de Radiología de Guatemala

Secretary, Dr. Carlos E. Escobar, 9ª, Calle A 0–05, Zona 1, Guatemala

Sociedad Mexicana de Radiología, A.C.

Coahuila No. 35, México 7, D.F., México.

Secretary-General, Dr. Jorge Cano Coquí. Meets first Monday of each month.

Sociedad Radiológica Panameña

Secretary, Dr. L. Arrieta Sánchez, Apartado No. 6323, Panamá, R. de P. Meets monthly in a department of radiology of a local hospital chosen at preceding meeting.

Sociedad Radiológica de Puerto Rico

Secretary, Dr. César Rosa, Box 9387, Santurce, Puerto Rico 00908. Meets second Thursday of each month at 8:00 P.M. at the Puerto Rico Medical Association Bldg. in San Juan.

BRITISH COMMONWEALTH OF NATIONS

Association of Radiologists of the Province of Quebec

121 Boul. Taschereau, Greenfield Park, P. Q., Canada. Meets four times a year.

British Institute of Radiology

Honorary Secretaries, D. H. Traspnell, M. Cohen, 32 Welbeck St., London, W1M/7PG, England.

Canadian Association of Physicists, Division of Medical and Biological Physics

Honorary Secretary-Treasurer, Dr. R. G. Baker, Ontario Cancer Foundation, Ottawa Civic Clinic, 1053 Carling Ave., Ottawa 3, Ont., Canada.

Canadian Association of Radiologists

Honorary Secretary, Dr. Ross O. Hill, Suite 806, 1440 St. Catherine St. West, Montreal 107, Que., Canada. Annual Meeting:

Edmonton and District Radiological Society

Secretary, Dr. L. A. Koller, Suite 360, Professional Bldg., 10830 Jasper Ave., Edmonton 15, Alberta, Canada. Meets third Thursday of each month October to May, except December, at various Edmonton Hospitals.

Faculty of Radiologists

Honorary Secretary, P. D. Thomson, 28 Portland Pl., London, W1N 4DE.

Montreal Radiological Study Club
Secretary, Dr. W. Paul Butt, Montreal General Hospital, Montreal, Que., Canada. Meets first Tuesday evening, October to April.

Section of Radiology of the Royal Society of Medicine (Confined to Medical Members)
Meets third Friday each month at 8:15 p.m. at the Royal Society of Medicine, 1 Wimpole St., London, W. 1 M8AE, 1 England.

Société Canadienne-Française de Radiologie
Secretary-General, Dr. Hubert Sasseville, Verdun Hospital, Montréal, P. Q., Canada. Meets every third Tuesday from October to April.

The Hospital Physicists' Association
Honorary Secretary, J. B. Massey, B.Sc., Christie Hosp. and Holt Radium Institute, Physics Department, Withington, Manchester M20 9BX, England.

Toronto Radiological Society
Secretary, Dr. George Wortzman, Toronto General Hosp., Toronto 12, Ont., Canada. Meets second Monday of each month, September through May.

The Royal Australasian College of Radiologists
Honorary Secretary, Dr. T. P. Loneragan, 45 Macquarie St., Sydney, N.S.W. 2000, Australia.

South America

Colégio Brasileiro de Radiologia
Secretary-General, Dr. José Marcos Pires de Oliveira, Caixa Postal 5984, São Paulo, Brazil.

Federación Argentina de Sociedades de Radiología
Branches of the Federation are: Sociedad de Radiólogos de la Provincia de Córdoba; Sociedad Argentina de Radiología; Asociación Argentina de Radiología; Sociedad de Radiología, Radioterapéutica y Medicina Nuclear de Rosario; Sociedad de Radiología y Medicina Nuclear del Centro y Sudeste de la Provincia de Buenos Aires (Mar del Plata); Sociedad Salteña de Radiología y Medicina Nuclear; Sociedad de Radiología de Tucumán; Sociedad de Radiologia del Nordeste Argentino; Sociedad de Radiología de La Plata; and Sociedad de Radiología de San Juan.
Secretary-General-Treasurer, Dr. Roberto Habichayn, Av. Colón 637, Córdoba, Argentina.
Congress will be organized by Sociedad de Radiología, Radioterapéutica y Medicina Nuclear de Rosario in 1975.

Sociedad Argentina de Radiología
Secretary-General, Dr. Alba de la Torre, Santa Fé 1171, Buenos Aires, Argentina. Meets first Wednesday evening, April through December.

Sociedad Boliviana de Radiología
Secretary, Dr. Javier Prada Méndez, Casilla 1182, La Paz, Bolivia. Meets monthly. General assembly once every two years.

Sociedade Brasileira de Radiologia
Secretary, Dr. Armando Rocha Amoêdo, Caixa Postal 1532, Rio de Janeiro, Brazil. General Assembly meets every two years in December.

Sociedade Brasileira de Radioterapia
Luiz Antonio, 644, São Paulo, Brazil. Meets monthly on second Wednesday at 9:00 p.m. in São Paulo at Av. Brigadeiro Luiz Antonio, 644.

Sociedad Chilena de Radiología
Secretary, Dr. Manuel Neira, Casilla 13426, Santiago, Chile. Meets first Friday of each month at Av. Santa María 1810 at 7:00 p.m.

Sociedad Colombiana de Radiología
Secretary-General, Dr. Gustavo Sánchez Sánchez, Bogotá, Colombia. Meets last Thursday of each month.

Sociedad Ecuatoriana de Radiología
Secretary, Dr. Luis Blum, Casilla 3712, Guayaquil, Ecuador.

Sociedad Paraguaya de Radiología
Secretary, Dr. Hugo Volpe Rios, 15 de Agosto 322, Asunción, Paraguay.

Sociedad Peruana de Radiología
Secretary-General, Dra. Ladis Delpino, Av. General Santa Cruz No. 315, Miraflores, Lima, Perú, Casilla Correo, 2306, Lima, Perú. Meets monthly except during January, February, and March.

Sociedad de Radiología del Atlantico
Secretary, Dr. Raul Fernandez, Calle 40 #41-110, Baranquilla, Colombia. Society meets monthly at the Instituto de Radiología.

Sociedad de Radiología del Nordeste Argentino
Secretary-General, Dr. Francisco J. Velar, Catamarca 561, Corrientes, Argentina.

Sociedad de Radiología de La Plata
Secretary, Dr. Hiram D. Haurigot, Calle 50 No. 374, La Plata, Argentina.

Sociedad de Radiología, Cancerología y Física Médica del Uruguay
Secretary-General, Dr. Manuel Gonzáles Maseda, Av. Agraciada 1464, piso 13, Montevideo, Uruguay.

Sociedade de Radiología de Pernambuco
Secretary, Dr. Manoel Medeiros Instituto de Radiologia da Faculdade de Medicina da Universidade do Recife, Caixa Postal 505, Pernambuco, Brazil.

Sociedad de Roentgenología y Medicina Nuclear de la Provincia de Córdoba
Secretary-General, Dr. Lucas C. Di Rienzo, Ave. Grl. Paz. 151, Córdoba, Argentina.

Sociedad de Radiología, Radioterapéutica y Medicina Nuclear de Rosario
Secretary-General, Dr. Federico Frágola, Santa Fe 1798, Rosario, Argentina.

Sociedad Salteña de Radiología y Medicina Nuclear
Treasurer, Dr. Julio Luis Baldi, Av. Sarmiento 536, Salta, Argentina.

Sociedad Venezolana de Radiología y Medicina Nuclear
Secretary-General, Dr. Salvador Itriago Borgas, Apartado Postal 9213, Candelaria, Caracas, Venezuela. Meets monthly, third Friday at Colegio Médico del Distrito Federal, Caracas.

Continental Europe

Österreichische Röntgen-Gesellschaft
Secretary, Dr. Ernst Kotcher, Wiener Allgemeine Poliklinik Mariannengasse 10, A-1090 Wien, Austria. Meets second Tuesday of each month in Allgemeine Poliklinik.

Société Royale Belge de Radiologie
General Secretary, Dr. Joseph Baeyens, Alost, Belgium. Meets in February, March, May, June, September, October, November and December.

Société Européenne de Radiologie Pédiatrique
Secretary, Dr. J. Corbaton, Clinica Infantil "La Paz," Av. Generalissimo, 117 Madrid 34, Spain. Annual Meeting:
Permanent Secretary, Clément Fauré, Hôpital des Enfants Malades, 149, rue de Sèvres, 75 730, Paris Cadet 15, France.

Société Française de Radiologie Médicale, Médecine Nucléaire et Électrologie, and its branches: Société du Sud-Ouest, du Littoral méditerranéen, du Centre et Lyonnais, du Nord, de l'Ouest, de l'Est, du Massif Central, d'Outre-Mer et d'Étranger. Parent Society meets third Monday of each month, except during July, August and September, rue de Seine 12, Paris, France.
Secretary-General, Dr. Ch. Proux, 9 rue Daru, Paris 75008, France.

Société Française de Neuroradiologie
Secretary-General, Professeur agr. R. Djindjian 16, rue de l'Université 75, Paris 7e, France. Annual meeting.

Československá Radiologická Společnost
Secretary, Associate Professor Jaromír Kolář, M.D., Sc.D., Radiological Clinic, Praha 2, U nemocnice 2, Czechoslovakia. Meets monthly except during July, August and September. Annual general meeting.

Deutsche Röntgengesellschaft
President, Professor Dr. med. Walter Frommhold, Director of Medizinisches Strahleninstitut der Universität Tübingen, Röntgenweg 11, 7400 Tübingen, Germany.

Faculty of Radiologists of the Royal College of Surgeons in Ireland
Honor. Secretary, Max. J. Ryan, St. Stephen's Green, Dublin 2. Annual Meeting:

Società Italiana di Radiologia Medica e Medicina Nucleare
Administrative Secretary, Prof. E. Conte, Ospedale Mauriziano, 10128 Torino, Italy. Meets annually.

Societas Radiologica Danica
Secretary, Dr. Bent Langenfeldt, Tretommervej 20a, DK. 8240 Risskov, Denmark.

Nederlandse Vereniging voor Radiologie
Secretary, Dr. J. D. Mulder, Dept. of Rad., Akademisch Ziekenhuis, Leiden, Netherlands.

Norsk Forening for Medicinsk Radiologi
General Secretary, Gunnar Stake, Rikshospitalet, Oslo, Norway.

Scandinavian Radiological Society
Secretary-General, Professor C. F. Unnérus, M.D., Hagalung-Tapiola, Havsvindsvägn 5 C., Finland. Annual Meeting.

Sociedad Española de Radiología y Electrología Médicas y de Medicina Nuclear
Secretary-General, Dr. Pilar Gallar Barberá, Villanueva, 11, Madrid 1, España. Meets every other Saturday evening of each month, Oct. to June, inclusive, in Madrid.

Sociedade Portuguesa de Radiologia e Medicina Nuclear
Secretary-General, Dr. Luís Aires de Sousa, Av. Elias Garcia, 123- 1, Esg.-Lisboa i-Portugal.

Svensk Förening för Medicinsk Radiologi
Secretary, Dr. Hanz Ringertz, Röntgendiagnostika Avdelningen, Karolinska Sjukhuset 104 01 Stockholm 60, Sweden.

Schweizerische Vereinigung für Radiologie, Nuklearmedizin und Strahlenbiologie (Association Suisse de Radiologie, Médecine Nucléaire et de Radiobiologie)
Secretary, Dr. med. Gustav Schoch, Bethesdaspital, Gellerstrasse 144, 4000 Basel, Switzerland.

Asia

Bengal Radiological Association
Honorary Secretary, Dr. B. Chatterji, 262 Rash Behari Ave., Calcutta 700019, India. Meets 1st Fri. and 3rd Wed. of every month.

Indian Radiological Association
Honor. Gen. Secretary, Dr. S. P. Aggarwal, 10-B Kasturba Ghandi Marg, New Delhi ii000i. 28th Indian Congress of Radiology will be held in Hyderabad in 1975.

Indonesian Radiological Society
Secretary, Dr. Gani Iljas Sasmitaatmadja, Radiology Dep., Faculty of Medicine, University of Indonesia, Salemba 6, Jakarta, Indonesia.

Iranian Radiological Society
Secretary, Dr. Majid Rooholamini, P.O. Box No. 14-1151, Teheran, Iran. The Society meets on the second Saturday of each month.

Israel Radiological Society
Secretary, Dr. M. A. Lerner, Hesharon Hosp., Petah-Tigva, Israel.

Philippine College of Radiology
Secretary-Treasurer, Dr. Eduardo V. Nievera, Box 1284 Commercial Center, Makati, Rizal D-708, Philippines. Meets every second Thursday of the month.

Radiological Society of Thailand
Secretary, Prof. Rojana Suvansuthi, M.D., Ph.D., Depart. of Rad., Sirizaj Hospital, Faculty of Medicine, Mahidol University, Bangkok 7, Thailand.

Africa

Association of Radiologists of West Africa
Honorary Secretary, C. A. Beetlestone, M.B., B.S., D.M.R.D., Dept. Radiol., University College Hosp., Ibadan, Nigeria.

Radiological Society of South Africa
Secretary, Dr. A. Visser, P. O. Box 8850, Johannesburg, South Africa.

South African International Radiological Congress
Director, Dr. Paul Sneider, P.O. Box 4878, Johannesburg, South Africa.

ABSTRACTS OF RADIOLOGIC LITERATURE

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ROENTGEN DIAGNOSIS

Head

Rzymski, Kazimierz, and Kosowicz, Jerzy. The skull in gonadal dysgenesis: a roentgenometric study. *Clin. Radiol.*, July, 1975, *26*, 379–384. (From: The Departments of Diagnostic Radiology and Endocrinology, School of Medicine, Poznań, Poland.)

The skull characteristics were studied in 54 patients with Turner's syndrome. The patients were 7–46 years of age and all were short in stature, measuring in the range of average 9–13 year old girls; therefore comparisons were made with eleven year old girls as well as with normal adults.

It was determined that the width of the skull and height of the cerebral portion were similar to those found in normal women; however, the facial bones and orbits were small, corresponding to those of eleven year old girls. The mastoid processes were smaller than in average eleven year old girls. In contrast to the small facial bones, the mandible in 50 percent of the patients was thick and frequently squared, resembling a man's jaw.

The bones of the vault were thin in 40 percent of cases and the sella was usually small. In 43 of 54 patients, the petroclinoid ligament was calcified before the age of 20. The sphenoid sinuses were often large and excessively pneumatized (78 percent). The angle of the skull base was increased (74 percent) and this increase was evident in the first decade. The authors postulate that the delay in epiphyseal fusion and deficiency of sex hormones in these patients may be responsible for the further growth of the mandible and excessive development of the paranasal sinuses.—*Martha Mottram, M.D.*

Pinto, Richard S., George, Ajax E., Koslow, Maxim, and Barasch, Gene. Neuroradiology of basal anterior fossa (transethmoidal) encephaloceles. *Radiology*, Oct., 1975, *117*, 79–85. (Address: Richard S. Pinto, M.D., Department of Radiology, Section of Neuroradiology, New York University Medical Center, 560 1st Avenue, New York, N. Y. 10016.)

Encephaloceles of the basal anterior fossa may be insidious in presentation and remain undetected until adulthood. Inadequate clinical and roentgenologic evaluation can lead to hasty surgical intervention, with serious medical and surgical implications.

Although the majority of encephaloceles occur occipitally, approximately 12 to 15 percent involve the anterior cranial fossa. Anterior basal encephaloceles are frequently transethmoidal, protruding through a defect in the lamina cribrosa.

Transethmoidal encephaloceles are best evaluated by first performing hypocycloidal tomography and then magnification carotid angiography.

Carotid angiography may demonstrate extracranial herniation of the anteroinferior frontal artery through the osseous defect. The anteroinferior frontal artery is a branch of the anterior cerebral artery complex which arises distal to the anterior communicating artery and may originate from a common trunk with the frontopolar artery. Herniation of the anteroinferior frontal artery through an osseous defect is diagnostic of extracranial herniation of brain tissue.

Pneumoencephalography is inconclusive as to the presence or absence of brain tissue within a demonstrated extracranial sac; however, it may show ventricular communication of the encephalocele and aid in the diagnosis of hydrocephalus. Anteroinferior displacement and tapering of the frontal horn at pneumoencephalography is an indirect sign of transethmoidal encephalocele.

RISA cisternography may establish the diagnosis of communicating hydrocephalus if pneumoencephalography fails to demonstrate a ventricular block in the face of ventricular dilatation.—*J. L. Montgomery, M.D.*

Osborn, J. D. A comparative study of special petrous views and tomography in the diagnosis of acoustic neuromas. *Brit. J. Radiol.*, Dec., 1975, *48*, 996–999. (From: Wessex Neurological Centre, Southampton General Hospital, Southampton, England.)

A series of 56 patients with acoustic neuromas and 60 normal control patients was examined. Each had conventional examinations of the skull, each had specific views of the petrous portions of the temporal bones, and each had tomograms of the internal auditory canals. The controls and the patients were matched for age and sex. The three sets of roentgenograms, conventional films, special views, and tomograms, were placed in separate envelopes and the entire series of 348 sets of films was examined at random. The criteria used were those established by Valvassori and include: widening of any portion of the canal by 2 mm in comparison with its fellow; demineralization; shortening of the posterior wall by 2–3 mm; and asymmetry in the falciform crest. Some of these criteria are shown only in tomograms.

The conventional examination consisted of lateral, anteroposterior, posteroanterior, half-axial and full-axial projections. The special petrous views consisted of slit perorbital, slit full-axial, slit half-axial, and "Stockholm C" projections (similar to Stenvers' projections). The tomograms were made 2 mm apart using 5 sections.

The study reveals that special petrous projections alone will discover 78 percent of patients with acoustic neuromas. Using tomography alone, 84 percent of acoustic neuromas are found. However, there is an accompanying increased incidence of false positives among the normal controls using tomography only, and this amounts to 10 percent, as compared with only 3.5 percent false positives using only the special petrous projections. In about 10 percent of patients with acoustic neuromas tomography is normal and thus cannot be relied upon to exclude the presence of the tumor.

The author believes that tomography cannot be considered an essential step in the investigation of patients suspected of having acoustic neuroma: however, it may resolve uncertainty about plain film studies.—*E. Frederick Lang, M.D.*

NECK AND CHEST

SINNER, W. N. Wert und Bedeutung der perkutanen transthorakalen Nadelbiopsie für die Diagnose intrathorakaler Krankheitsprozesse: Technik, Indikationen, Resultate und Komplikationen. (The value and use of percutaneous trans-thoracic needle biopsy in the diagnosis of intra-thoracic disease: technique, indications, results and complications.) *Fortschr. a. d. Geb. d. Röntgenstrahlen u. d. Nuklearmedizin*, Sept., 1975, *123*, 197–202. (Address: Vis. Ass. Professor, University of Miami, Department of Radiology, Jackson Memorial Hospital, School of Medicine, P.O. Box 520875, Biscayne Annex, Miami, Fla. 33152.)

In the thirteen years between 1961 and 1974, 2,726 patients with localized intrathoracic disease were subjected to trans-thoracic needle biopsy, with a total of 5,300 biopsies made under fluoroscopic control.

The indications for the examination include investigation of localized intrathoracic disease which cannot be classified by conventional techniques, such as cytological examination of the sputum, bronchoscopy, and mediastinoscopy. Patients are examined to permit cytologic diagnosis, as in the case of the differentiation of benign or malignant nodule; identification of metastasis, as contrasted with a primary tumor; to determine operability in the presence of bilateral disease; and to verify the benign nature of processes, such as hematoma, cyst, tuberculosis and other granulomas, as well as classifying unresolved pneumonia, infarction, abscess, and similar processes. The test is useful in classifying asymptomatic operable lesions which have appeared in the interval between two roentgen examinations.

There are contraindications to the examination, such as diseases which might be spread by the biopsy. Such diseases are bronchiectasis, vascular anomalies, and pulmonary sequestration. These are usually better examined by other methods. Any echinococcus cyst should not be punctured. The examination is not recommended in patients over 70 years of age, in patients in poor general condition, and in those with increased bleeding time. The studies should not be carried out on both lungs in one session.

A definite diagnosis could be made in 90.7 percent of the 2,726 patients. Primary malignancy was encountered in 39 percent of the successful examinations and metastasis was discovered in 7.4 percent. In 50.8 percent, benign changes, such as specific and non-specific chronic infection, benign tumors, pseudo-tumors, and cysts were classified histologically.

The commonest complication was pneumothorax which was seen in 27.2 percent, and two-thirds of these required no treatment. In the other third, aspiration either by needle or tube was carried out. In 11 percent, localized bleeding was encountered with complete reabsorption of this in a few days. Hemoptysis occurred in about 2 percent. One patient, a 73 year old, with an undifferentiated pleural mesothelioma, developed subcutaneous metastatic implants of histology similar to the original tumor a few months following biopsy. In this series of patients, no air embolus occurred.

The method is of particular value in improving the prognosis in a large group of patients with bronchial carcinoma in the preclinical stage.—*E. Frederick Lang, M.D.*

GENITOURINARY

CERNY, J. C., FARAH, R., RIAN, R., and WECKSTEIN, M. L. An evaluation of lymphangiography in staging carcinoma of the prostate. *J. Urol.*, 1975, *113*, 367–370. (Address: Henry Ford Hospital, Detroit, Michigan.)

Pedal lymphangiography was done on 38 patients with stages 0, A and B carcinoma of the prostate. The lymphangiograms were positive in 19 cases and negative in 19. Of 18 patients who underwent lymphadenectomy (9 with positive and 9 with negative studies) operative findings confirmed the lymphangiogram in 15 (83 percent).

In the 6 patients with osseous metastases and/or enzyme elevation, the lymphangiogram was positive. Furthermore, 13 patients with positive lymphangiograms had negative osseous and enzyme survey, emphasizing that nodal involvement may be the earliest finding in disseminated carcinoma of the prostate. The value of lymphangiography in staging carcinoma of the prostate prior to radical prostatectomy or irradiation seems well established.—*Authors' Abstract* (permission Williams & Wilkins)

WAJSMAN, Z., BAUMGARTNER, G., MURPHY, G. P., and MERRIN, C. Evaluation of lymphangiography for clinical staging of bladder tumors. *J. Urol.*, 1975, *114*, 712–714. (Address: University of New York, Buffalo, New York.)

Preoperative lymphangiography was done on 18 patients with bladder cancer and the results were correlated with the surgicopathological findings at the time of radical cystectomy and pelvic lymph node dissection. Correlation between radiological and pathological findings showed no falsely negative results. One patient had a falsely positive interpretation of lymphangiography. The accuracy of the study was 94 percent. Accurate interpretation of lymphography is related to the experience of the reader. Routine use of lymphangiography in clinical staging of bladder cancer is recommended.—*Authors' Abstract* (permission Williams & Wilkins)

NABER, K. G., KUNI, H., and MADSEN, P. O. Continuous infusion urography in unilateral hydronephrosis. *J. Urol.*, 1975, *113*, 337–342. (Address: University of Marburg, Germany.)

In cases of unilateral hydronephrosis the urine concentration of contrast medium, for example diatrizoate, depends on the remaining renal function, the rate of turnover in the obstructed renal pelvis and the function of the contralateral kidney. Contrast medium for a single injection or a short infusion time is rapidly excreted by the normal contralateral kidney, without allowing high enough plasma levels long enough for sufficient urine concentrations in the hydronephrotic kidney. This excretion rate can be compensated for by continuous infusion urography for several hours with large doses of contrast medium (up to 1,250 ml 30 percent diatrizoate). This method was theoretically computerized, tested in animal experiments and clinically used in 11 patients. It can improve the diagnostic possibilities of excretory urography, especially in cases of unilateral obstruction, and can minimize the need for retrograde pyelography with its known complications.—*Authors' Abstract* (permission Williams & Wilkins)

BEN-MENACHEM, Y., CRIGLER, C. M., and CORRIERE, J. N., JR. Elective transcatheter renal artery occlusion prior to nephrectomy. *J. Urol.*, 1975, *114*, 355–359. (Address: University of Texas Medical School, Houston, Texas.)

An hour before nephrectomy 10 patients with hypernephroma and 2 with pyonephrosis underwent occlusion of the renal arteries with gelfoam via selective catheterization, using the Seldinger percutaneous technique. This technique facilitated the operation by collapsing the renal and perirenal veins, decreased blood loss and prevented the dissemination of tumor cells or septic emboli from organ manipulation.

Premedication for nephrectomy is given at the beginning of the procedure and the patient is transferred to the operating room immediately after its conclusion. Pain is usually negligible in the first hour after occlusion but a delay in operation for more than 4 hours will usually result in severe pain and considerable suffering to the patient. For this reason, the occlusion is not performed during the original angiographic study but is delayed until immediately before the operation.—*Authors' Abstract* (permission Williams & Wilkins)

NERVOUS SYSTEM

SAGE, M. R., MCALLISTER, V. L., KENDALL, B. E., BULL, J. W. D., and MOSELEY, I. F. Radiology in the diagnosis of colloid cysts of the third ventricle. *Brit. J. Radiol.*, 1975, *48*, 708–723. (Address: The National Hospital for Nervous Diseases, Queen Square, London, W.C.1, England.)

A series of 38 cases of colloid cyst of the 3rd ventricle is described in most of whom the diagnosis, important for curative surgery, was made radiologically. The most useful investigative technique was pneumography, by which the tumor was outlined in almost all cases. The lateral "hanging head" projection generally demonstrated the lesion most satisfactorily. Care in manipulating air introduced at ventriculography through the foramina of Monro into the 3rd ventricle was frequently rewarded by clear definition of the tumor. In more than one-third of the cases, the lateral plain skull radiograph showed truncation of the dorsum sellae indicative of chronic obstructive hydrocephalus, and, in the large majority of these, pneumography confirmed that the 3rd ventricle, rather than the interventricular foramen, was the site of obstruction to the drainage of cerebrospinal fluid. Carotid angiography, showing hydrocephalus, and in the same cases elevation and lateral displacement of the anterior portion of the internal cerebral veins, yielded strong supportive evidence. Vertebral angiography was less specific, and isotope scanning was not helpful.—*Authors' Abstract*

WILBRAND, H. F., and BERGSTRÖM, B. Multidirectional tomography of defects in the facial canal, an experimental investigation. *Acta radiol.* [*Diag.*], 1975, *16*, 223–240. (Address: University of Uppsala, S-750 14 Uppsala, Sweden.)

Defects in the facial canal, either natural or of pathologic origin, may endanger the facial nerve in middle ear surgery.

A defect or dehiscence of the canal, when preexistent, is caused by a developmental disturbance (BAST *et al.* 1956). The risk of inflammatory spread through such defects has been discussed for quite a long time. The same applies to lesions of the canal due to cholesteatoma. When these lesions are located to the cochlear process, the facial sinus or the lateral knee, their demonstration is of particular importance. The trend in otosurgery today is not only to eliminate lesions but also to restore impaired hearing. This has led to refined surgical procedures, which have necessitated more detailed demonstration of the anatomy. Defects in the wall of the facial canal entail a risk of immediate or delayed facial paralysis caused by trauma to the nerve in middle ear surgery, *e.g.*, radical mastoidectomy, stapedectomy, tympanoplasty, fenestration and eighth nerve section.

An attempt was made to determine to what extent defects in the tympanic part of the facial canal might be demonstrated by tomography. No such experimental investigation appears to have been performed previously. In a series of 21 temporal bones surgical defects were created and the fresh specimens were subsequently tomographed both in the isolated state and mounted in a skull phantom. The results show that defects with dimensions of surgical interest can be revealed tomographically provided that the wall is not exceedingly thin. Several other factors are decisive for demonstration of the defects, such as the anatomic location, tomographic positioning, equipment and technique.

Essential anatomic factors are the course of the canal, the dimension of the defect and the absorption factor of the environmental structures. The half axial or an intermediate projection between this and the axial-pyramidal is to be preferred. In hypocycloid and spiral tomography a small focal spot size and low tube potentials (50 to 65 kV) are recommended and when feasible the use of a high definition screen-film system. With regard to the section thickness of the canal in both the Polytome and Stratomatic a distance between the sections of 0.5 mm is needed to guarantee overlapping of the structural details in the tomograms. It is assumed that minor defects are concealed by tomographic phenomena such as spurious contours or superimposition from neighboring structures. The experience gained from these experiments is directly applicable to clinical tomography.

HINDMARSH, T. Lumbar myelography with meglumine iocarmate and metrizamide. *Acta radiol.* [*Diag.*], 1975, *16*, 209–221.

Metrizamide and meglumine iocarmate (Dimer-X), which at present are the contrast media for myelography best tolerated by the central nervous system, were compared in a double-blind test comprising a total of 86 patients, all with symptoms of lumbar or sacral root involvement. Symptoms appearing were recorded using a standard interview formula 24 hours after myelography. EEG, routine laboratory analyses of CSF and neurologic examinations were also made. In some cases CSF paper electrophoresis, CSF pressure recordings and determination of CSF iodine content were obtained.

Metrizamide, although not completely inert, is better tolerated by the central nervous system than meglumine iocarmate and should be preferred for lumbar myelography. Metrizamide and meglumine iocarmate both rank high with regard to the quality of diagnostic information, and—provided that the iodine concentration is the same—seem equal in this respect.—*Author's Abstract*

ULTRASONICS

WATTS, E., NOMEIR, A. M., and BARNES, R. Echocardiography in evaluation of mitro valve prostheses. *J. Clin. Ultrasound*, 1975, *3*, 111. (Address: Department of Medicine and the Sonic Laboratory, Bowman Gray School of Medicine, Winston-Salem, North Carolina.)

Thirty-three patients with mitral valve prostheses were studied with echocardiography in an effort to determine if this technique could be useful in detecting significant abnormalities. Recordings were obtained in the supine position with the transducer directed to record maximum excursion of the prosthesis. Echoes from the struts, poppet and sewing ring were readily recorded. Amplitude of excursion and opening and closing velocities of the poppet were measured. Fifty echocardiographic recordings were obtained from the 33 patients. Of the 33 patients studied, 22 were thought to have "normal" echo tracings while in 11, the tracings were considered "abnormal." Apparent abnormalities consisted of: (1) abnormal diastolic separation between the poppet and strut, (2) increased echoes near the poppet, strut or sewing ring, and (3) a combination of both. There was only one instance of suspected "sticking" of the prosthesis. All patients who had "abnormal" studies except one developed complications associated with their prosthesis (90 percent) compared to only 36 percent in patients with "normal" tracings. Five patients in each group died. Autopsy studies are described and correlations with the echocardiographic findings are made. In low profile valves reduction in excursion of the disc may be an indication of malfunction.—*Authors' Abstract*

GOLDBERG, B. B., POLLACK, H. M., CAPITANIO, M. A., and KIRKPATRICK, J. A. Ultrasonography: an aid in the diagnosis of masses in pediatric patients. *Pediatrics*, 1975, *56*, 421–428. (From: Departments of Radiology, Episcopal Hospital and St. Christopher's Hospital for Children, Philadelphia, Pennsylvania.)

Ultrasound was used to evaluate 100 pediatric patients suspected of having a mass. This technique was found to be useful in several ways: (1) differentiation of cystic, solid, and complex masses, which is not usually possible with routine roentgenographic evaluation; (2) delineation of free fluid collections from those that are loculated or contained within masses; (3) measurement of the size of both normal and abnormal structures; and (4) confirmation of the abnormal position or absence of organs.—*Authors' Abstract*

SCHUCHMAN, H., FEIGENBAUM, H., DILLEN, J. C., and CHANG, S. Intracavitary echoes in patients with mitral prosthetic valves. *J. Clin. Ultrasound*, 1975, *3*, 107. (Address: Indiana University School of Medicine, Indianapolis, Indiana 46202.)

In the course of doing routine echocardiograms on patients with mitral prosthetic valves, we observed peculiar intracavitary echoes within the left ventricle. Of the 36 valves studied in 31 different patients, 14 echocardiograms demonstrated the abnormal intracavitary echoes and 22 did not. The presence of mitral insufficiency, atrial fibrillation, systemic emboli and warfarin sodium (Coumadin) therapy were roughly equal in the two groups. A higher percentage of abnormal intracavitary echoes occurred in patients with a hemoglobin less than 11 gm/100 ml, other prosthetic valves, cloth covered valves, low platelets, and functional class III-IV. Although this study does not clarify the origin of these abnormal echoes, it is possible that they originate from particulate matter such as tiny clots or fibers from the cloth covering of the valve.—*Authors' Abstract*

EGEBLAD, H., BANG, J., and NORTHEVED, A. Ultrasonic identification and examination of fetal heart structure. *J. Clin. Ultrasound*, 1975, *3*, 95. (Address: Hybenvej 40, 2830 Virum, Denmark.)

Ultrasonic studies were performed on normal fetuses ranging from 36 to 40 weeks gestational age in an attempt to visualize anatomical details of the fetal heart. We were able to visualize cardiac structures hitherto thought to be unidentifiable. Two-dimensional B-scan exposures of sections showed transverse and longitudinal sections of the fetal heart, including the cardiac septa and inlet and outlet sites of the large vessels. To attempt to elucidate the dynamics of the fetal heart, the motility patterns of the cardiac structures were examined by time-motion mode scanning and the patterns obtained were compared to those observed in the postnatal heart.—*Authors' Abstract*

MARICH, K. W., ZATZ, L. M., GREEN, P. S., SUAREZ, J. R., and MACOVSKI, A. Real-time imaging with a new ultrasonic camera: part I, *in vitro* experimental studies on transmission imaging of biological structures. *J. Clin. Ultrasound*, 1975, *3*, 5. (Address: Stanford Research Institute, Menlo Park, California 94025.)

Results are described of *in vitro* biological experimentation using a new through-transmission ultrasonic camera system developed at the Stanford Research Institute. The camera system produces real-time focused, orthographic images of a 15×15 cm field. The *in vitro* studies, which demonstrate the diagnostic potential of the new technique, include transmission images of selected excised organs such as liver, kidney, spleen, and uterus. In addition, preliminary studies evaluating ultrasonic image quality and the effect of out-of-focus structures are presented.—*Authors' Abstract*

ZATZ, L. M., MARICH, K. W., GREEN, P. S., LIPTON, M. J., SUAREZ, J. R., and MACOVSKI, A. Real-time imaging with a new ultrasonic camera: part II, preliminary studies in normal adults. *J. Clin. Ultrasound*, 1975, *3*, 17. (Address: Stanford Research Institute, Menlo Park, California 94025.)

A new transmission ultrasound camera system has provided focused images in real time through the abdomen of adult volunteers at average incident sound intensity levels of less than 1 mW/cm^2. The camera uses a unique acousto-mechanical lens/deflection system and a linear array of piezoelectric transducers to detect the ultrasound image. Bony structures and costal cartilages were clearly seen. The colon was regularly seen and the kidney could be outlined in several subjects. The stomach and duodenal bulb were demonstrated and peristalsis was observed using a barium contrast material. The camera has the potential of extending the use of ultrasound in clinical medicine by providing an ultrasound soft tissue imaging system analogous to an x-ray fluoroscope. The need for further clinical evaluation and research to improve these images is emphasized.—*Authors' Abstract*

WEILL, F., EISENSCHER, A., AUCANT, D., BOURGOIN, A., and GALLINET, D. Ultrasonic study of venous patterns in the right hypochondrium: an anatomical approach to differential diagnosis of obstructive jaundice. *J. Clin. Ultrasound*, 1975, *3*, 23. (Address: Service central de Radiologie, Departement de diagnostic, 2 Place St. Jacques, 25000 Besançon, France.)

Through real time ultrasonography, it is possible to display the splenic vein, the superior mesenteric vein, the vena porta, and the intrahepatic portal and systemic veins. In jaundice, it is of the utmost importance to carefully identify the vena porta before making a diagnosis of common bile duct enlargement. It is also necessary, when confronted with a pattern of apparently enlarged intrahepatic ducts, to conduct a thorough study of possible confluences of the ducts with the vena porta or vena cava to be certain that the ducts are not part of the portal or systemic venous network. Without such differentiation, portal enlargement caused by portal hypertension, systemic venous enlargement caused by cardiac insufficiency, or even nonpathological wide veins may lead to an erroneous conclusion that obstructive jaundice is present.—*Authors' Abstract*

DALLOW, R. L. Evaluation of unilateral exophthalmos with ultrasonography: analysis of 258 consecutive cases. *Laryngoscope*, 1975, *85*, 1905–1919.

Ultrasound examination has emerged as a valuable technique for defining soft tissue abnormalities of the eye and orbit. As high frequency sound waves (5 to 20 megahertz) are projected through soft tissues, echoes are produced at tissue interfaces. These echoes are displayed on oscilloscopes as either one-dimensional amplitude spikes (A-mode ultrasonography), or as dots integrated into a two-dimensional image representing a thin section through the entire orbit (B-scan ultrasonography). A-mode indicates tissue substance, while B-scan illustrates tissue morphology.

With this technique, orbital tumors are clearly distinguished in terms of their location, size, and configuration, as well as the basic tissue type (cystic, solid, angiomatous or infiltrative). Other orbital processes are defined by ultrasonography also, including inflammatory conditions such as diffuse pseudotumor or cellulitis, congestive conditions such as dysthyroid exophthalmos, and orbital hemorrhage. Intracranial and vascular etiologies of exophthalmos have no specific ultrasound signs.

In a series of 258 consecutive patients with unilateral exophthalmos examined with ultrasonography, diagnosis of tumor was made in 26 percent (66 cases). Over-all accuracy of orbital tumor diagnosis by ultrasonography was 94 percent in this series. Tumor localization, configuration, and extent indicated by the test aided in selecting surgical approaches. Other patients in the series were diagnosed ultrasonically as a variety of other entities, mostly inflammatory and dysthyroid exophthalmos. Normal ultrasound studies were found in 19 percent. None of these patients had subsequent diagnosis of tumor.

Diagnostic ultrasonography is capable of detecting orbital tumors and distinguishing them from inflammatory, congestive, and other causes of exophthalmos with a high degree of reliability. The test is painless, well tolerated, non-invasive, and non-toxic. It now has a prominent role in evaluation of any patient with exophthalmos.—*Author's Abstract*

RADIATION THERAPY

FLETCHER, G. H., LINDBERG, R. D., HAMBERGER, A., and HORIOT, J. C. Reasons for irradiation failure in squamous cell carcinoma of the larynx. *Laryngoscope*, 1975, *85*, 987–1003.

The reasons for irradiation failure in squamous cell carcinoma of the larynx can be:

1. Geographical miss because of undiagnosed extensions is the exception. Almost all of the recurrences were well within the treatment portals.
2. Specific extensions with an unfavorable tumor bed. Extension of disease into poorly vascularized structures and/or deep infiltration with fixation are causes of failure.
3. Low dose for the volume cancer. Higher doses delivered in longer treatment time are necessary for 90 percent control of bulky exophytic supraglottic lesions.
4. Techniques which do not assure daily coverage of the tumor. With carefully drawn and checked anatomical portals, geographical misses should be nonexistent.
5. Sigmoid response curve. There is an 85 percent control of the T_1 glottic tumors. The control rate is 90 percent of the T_1 and T_2 supraglottic tumors, and the 10 percent failures have no obvious explanation except that the plateau of the sigmoid response curve has been reached. A negligible yield would be obtained by increasing doses which would not be justified because of concomitant increase in frequency and severity of complications and lessening of the quality of voice.
6. New cancer. Probably 25 percent of the so-called recurrences on the vocal cords are actually new primary lesions.—*Authors' Abstract*

RADIATION BIOLOGY

CHASKES, S., KINGDON, G. C., and BALISH, E. Serum immunoglobulin levels in humans exposed to therapeutic total-body gamma irradiation. *Radiat. Res.*, 1975, *62*, 145–158. (Address: Medical Division, Oak Ridge Associated Universities, Oak Ridge, Tennessee 37830.)

Reduced serum immunoglobulin (IgA, IgG, IgM) levels developed in the majority of 27 patients with hematologic disorders after treatment with 100–350 R total-body gamma-ray exposures at a dose rate of either 1.5 R/min to 1.5 R/hr. A reduction in IgA of 20 percent or more was found in 66 percent of the cases, while 56 percent showed an IgM decrease, and 49 percent an IgG decrease of 20 percent. The severity of immunoglobulin depression was influenced by the total radiation dose and the patient's primary disease. The occurrence of IgG and IgM depression was greater when the radiation was given at 1.5 R/hr than when the dose rate was 1.5 R/min. Substantial but incomplete recovery toward preirradiation immunoglobulin levels was found for most patients by 7 weeks following total-body irradiation (TBI).—*Authors' Abstract*

GOH, K. O. Total-body irradiation and human chromosomes. IV. Cytogenetic follow-up studies 8 and 10½ years after total body irradiation. *Radiat. Res.*, 1975, *62*, 364–373. (Address: Medical Division, Oak Ridge Associated Universities, Oak Ridge, Tennessee 37830.)

Chromosomal breaks and abnormal chromosomes were found in the peripheral blood and bone marrow cultures from six persons who were accidentally exposed to total-body irradiation 8 and 10½ yr previously. These types of abnormalities were found in these same patients by Bender and Gooch 2½ yr and 3½ yr after the radiation exposure and by us 7 yr after the accident. The frequencies of the abnormalities remain higher than the normal controls. There is good evidence that there is an increased incidence of cancer and leukemia among populations exposed to radiation. It has been suggested that chromosomal aberrations are involved in the development of some cancer or leukemia in irradiated persons. However, none of our patients has these diseases. It is possible that the development of clinical cancer or leukemia (phenotype) depends not only on the presence of abnormal cells (genotype), but also on factors that favor these abnormal cells.—*Author's Abstract*

KAL, H. B., BARENDSEN, G. W., HAUWE, R. B. V., and ROELSE, H. Increased radiosensitivity of rat rhabdomyosarcoma cells induced by protracted irradiation. *Radiat. Res.* 1975, *63*, 521–530. (Address: Radiobiological Institute TNO, 151 Lange Kleiweg, Rijswijk [ZH], The Netherlands.)

Cells of a solid rat rhabdomyosarcoma, which can be cultured *in vitro* and upon inoculation grow *in vivo* into new tumors, were irradiated at low dose rates *in vitro* or *in vivo*. Assays of fractions of clonogenic cells show that repair of sublethal damage takes place during protracted irradiation. Nevertheless an acute single dose administered at the end of a protracted irradiation of many hours is more effective with respect to induction of cell lethality than a single acute dose applied without pretreatment. This increased radiosensitivity at the end of a low dose rate treatment can be explained however by the observation based on DNA measurements, that cells were redistributed over the cell cycle phases with a relatively larger number of cells in the G_2+M phase.—*Authors' Abstract*

BRUNER, A., BOGO, V., and JONES, R. K. Delayed match-to-sample early performance decrement in monkeys after ^{60}Co irradiation. *Radiat. Res.*, 1975, *63*, 83–96. (Address: Lovelace Foundation, Albuquerque, New Mexico 87115.)

Sixteen monkeys were trained on a delayed match-to-sample task (DMTS) based on shock avoidance and irradiated with single, whole-body exposures of from 396 to 2000 rad ^{60}Co (midbody dose) at between 163 and 233 rad/min. Pre- to post-irradiation performance changes were assessed using a penalty-scaling measure which differentially weighted incorrect responses, response omissions, and error-omission sequences. Thirteen of the animals displayed early performance decrement, including five incapacitations, at lower doses (<1000 rad) than heretofore found effective. This was considered a function of task complexity, measurement sensitivity, and gamma effectiveness. The minimum effective midbody dose for inducing decrement using the DMTS task was estimated to be on the order of 500 rad. The nature of early, transient performance decrement seems to reflect more an inability to perform than an inability to perform correctly.—*Authors' Abstract*

RUGH, R., GINNS, E. I., HO, H. S., and LEACH, W. M. Responses of the mouse to microwave radiation during estrous cycle and pregnancy. *Radiat. Res.*, 1975, *62*, 225–241. (Address: Food and Drug Administration, Bureau of Radiological Health, Division of Biological Effects, Rockville, Maryland 20852.)

A new facility for microwave irradiation of mice which will provide reproducible dosimetry is described. The waveguide used provided the integral dose rate to experimental animals under stable and controlled environmental conditions of relative humidity and temperature, variables which have been found to be critical in microwave studies. In terms of average absorbed lethal dose, the female mouse was found to be more sensitive to microwave irradiation during estrus than during diestrus. Teratogenesis (*e.g.*, exencephalies) after sublethal irradiation of pregnant mice at 8 gestation days resulted from absorbed doses within the range of 3–8 calories per gram of body weight, and was never an all-or-none response. The incidence and variety of effects produced (hemorrhage, resorption, stunting, and fetal death) indicate that the cause and effect relationships are neither linear nor well enough established and understood to permit prediction of the biological effects either in the mouse or other species. As the absorbed dose of radiant energy is increased to the 8 day pregnant mouse, the probability of it producing at least one exencephaly is likewise increased. Nevertheless, the determination of the absorbed dose of microwave energy in each mouse is one step closer to determining the precise absorbed-dose—effect relationship for microwave exposures. A total of 1096 mice was exposed to microwave radiation and separately monitored in order to gather the related data.—*Authors' Abstract*

PHYSICS

GENANT, H. K., DOI, K., and MALL, J. C. Optical versus radiographic magnification for fine-detail skeletal radiography. *Invest. Radiol.*, 1975, *10*, 160–172. (Address: University of California, San Francisco, California 94143.)

Fine-detail radiographic techniques for peripheral skeletal imaging have gained wide clinical acceptance. In this study, the imaging properties and clinical applications of the optical magnification technique, which employs fine-grain industrial film and a large focal spot, are compared quantitatively and qualitatively with those of three slow screen-film techniques, namely, contact exposure with a large focal spot, 2× radiographic magnification with a 0.3 mm focal spot, and 4× radiographic magnification with a 50 μ focal spot. The modulation transfer functions (MTF's) of the recording systems and focal spots are obtained and film sensitometry performed. Clinical comparisons are made for patients with metabolic, arthritic and neoplastic skeletal disorders. The results illustrate the superiority of the optical magnification technique over contact or 2× magnification techniques using slow screen-film systems. If a microfocus tube is used, however, direct radiographic magnification may provide images comparable in resolution, noise and contrast to those made with the optical magnification technique, with lower radiation exposure to the patient.—*Authors' Abstract*

NUCLEAR MEDICINE

HANDMAKER, H., YOUNG, B. W., and LOWENSTEIN, J. M. Clinical experience with ^{99m}Tc-DMSA (dimercaptosuccinic acid), a new renal-imaging agent. *J. Nuclear Med.*, 1975, *16*, 28. (Address: Children's Hospital of San Francisco, San Francisco, California.)

Sixty-five patients were studied using the ^{99m}Tc-DMSA and a gamma scintillation camera (Table 2). In all but three patients the images obtained were of sufficient quality to satisfy the clinical question asked. Twenty-seven patients had renal studies with ^{99m}Tc-Sn-DTPA and 21 had ^{131}I-hippuran studies. In no instance was the renal image obtained with these other agents equal to or better than that obtained with the DMSA (Fig. 2). Excellent correlation was obtained in all cases compared with excretory urography and arteriography.—*Authors' Abstract*

LUNIA, S., PARTHASARATHY, K. L., BAKSHI, S., and BENDER, M. A. An evaluation of ^{99m}Tc-sulfur colloid liver scintiscans and their usefulness in metastatic workup: a review of 1,424 studies. *J. Nuclear Med.*, 1975, *16*, 62. (Address: Roswell Park Memorial Institute and State University of New York, Buffalo, New York.)

To determine the clinical usefulness of liver scintiscanning in detecting metastatic disease of the liver, 1,424 liver studies performed on 1,115 patients were reviewed along with their charts. Five hundred eighty-one patients had histopathological evaluation by needle biopsy of the liver, laparotomy, and/or autopsy within a mean period of 40 days of liver scan. The histopathological findings were correlated with the liver scintiscan findings and the latter gave an over-all accuracy of 77.3 percent.

In practice, multiple factors influence resolution capability of the instrument, especially when evaluating an organ like the liver. The important factors are: (a) the size of the organ with the possible occurrence of deep-seated lesions surrounded by thick normal liver tissue, (b) the motion of the liver during respiration which may obscure the delineation of the lesion (6, 15), (c) concomitant pathology such as interference from ascites, and (d) instrumentation errors.—*Authors' Abstract*

ADLER, S., PARTHASARATHY, K. L., BAKSHI, S. P., and STUTZMAN, L. Gallium-67-citrate scanning for the localization and staging of lymphomas. *J. Nuclear Med.*, 1975, *16*, 255. (Address: Roswell Park Memorial Institute, New York State Department of Health, Buffalo, New York.)

One-hundred and eight ^{67}Ga-citrate scans were evaluated in Hodgkin's and non-Hodgkin's lymphomas for staging, diagnosis of recurrence, and for determining the results of treatment. Accuracy as confirmed by comparing the scans with pathologic material or roentgenologic and clinical findings was found to be 83 percent. Known lymph node involvement was diagnosed correctly in 87 percent but accuracy was only 48 percent for extranodal areas. Bone lesions were diagnosed correctly in 83 percent compared with only 48 percent of lesions of the lungs and liver. Scans were 75 percent accurate in 28 patients scanned for initial staging. False negatives were present in 12 percent; recurrent tumor in an area of prior radiation therapy appeared to be the most common cause. There were 5 percent false positives. Gallium scanning is a useful adjunct to other modalities of detecting lymphoma.—*Authors' Abstract*

ZWEIMAN, F. G., HOLMAN, B. L., O'KEEFE, A., and IDOINE, J. Selective uptake of ^{99m}Tc complexes and ^{67}Ga in acutely infarcted myocardium. *J. Nuclear Med.*, 1975, *16*, 975. (Address: Harvard Medical School, Boston, Massachusetts.)

The suitability of various radiopharmaceuticals (^{99m}Tc-tetracycline analogs, ^{99m}Tc-glucoheptonate, ^{99m}Tc-diphosphonate, and ^{67}Ga-citrate) for use in imaging acute myocardial infarction was assessed by determining their biologic distributions in experimentally infarcted dogs. The highest infarct-to-normal myocardial concentration ratio was found with ^{99m}Tc-diphosphonate (27.9:1); the highest infarct-to-liver ratio was also found with ^{99m}Tc-diphosphonate (15.9:1). The infarct-to-bone ratio, however, was 0.4:1 with ^{99m}Tc-diphosphonate. There was an excellent positive linear correlation between blood-flow reduction and uptake of the radiopharmaceutical after a threshold reduction in blood flow with ^{99m}Tc-glucoheptonate and ^{99m}Tc-tetracycline. Technetium-99m-tetracycline accumulated only in infarcted tissue while ^{99m}Tc-diphosphonate was increased in both ischemic and infarcted tissue. Thus, ^{99m}Tc-diphosphonate has characteristics best suited for scintigraphic imaging. Since ^{99m}Tc-tetracycline accumulates only in infarcted tissue, however, this tracer more accurately defines the actual size of an acute infarction.—*Authors' Abstract*

Mori, T., Hamamoto, K., Onomama, Y., and Torizuka K. Tumor imaging after administration of ^{99m}Tc-labeled bleomycin. *J. Nuclear Med.*, 1975, *16*, 414. (Address: Kyoto University School of Medicine, Kyoto, Japan.)

Bleomycin, an anticancer drug, was labeled with ^{99m}Tc using stannous chloride and ascorbic acid and specific activities of 1–3 mCi/mg-eq with labeling efficiencies of 50–75 percent were achieved. Very rapid excretion of ^{99m}Tc-bleomycin through the kidney and concomitant rapid decrease of radioactivity in blood, various tissues and organs, and whole body were observed after intravenous administration of the radiopharmaceutical into tumor-bearing mice. In such animals, approximately 1 percent of the label was found in a transplanted fibrosarcoma within 30 min while 0.58 percent was recovered in such lesions even after 24 hr. In patients positive tumor images were obtained by scintigraphy as early as 1 hr after intravenous administration of 3–5 mCi of ^{99m}Tc-bleomycin. A total of 142 cases was examined by scintigraphy after administration of ^{99m}Tc-bleomycin and/or ^{67}Ga-citrate. In 93 cases with various malignant tumors, tumor was detected in 80 percent using ^{99m}Tc-bleomycin and in 63 percent using ^{67}Ga-citrate. Technetium-99m-bleomycin scintigraphy successfully detected tumors of the thyroid, lung, face, breast, extremity, and digestive tract and was also useful in finding metastatic lesions and brain tumors. However, ^{67}Ga scintigraphy gave superior results in detecting lesions in patients with malignant lymphomas. In patients with inflammatory diseases, accumulation in lesions was detected in 13 percent using ^{99m}Tc-bleomycin and in 48 percent using ^{67}Ga-citrate. The further use of ^{99m}Tc-bleomycin scintigraphy for tumor detection appears to be warranted.—*Authors' Abstract*

Berman, D. S., Salel, A. F., DeNardo, G. L., Bogren, H. G., and Mason, D. T. Clinical assessment of left ventricular regional contraction patterns and ejection fraction by high-resolution gated scintigraphy. *J. Nuclear Med.*, 1975, *16*, 865. (Address: University of California School of Medicine, Davis, California.)

An improved, noninvasive, radionuclidic, gated blood-pool imaging technique has been developed for clinical analysis of regional contraction abnormalities of the left ventricle and determination of ejection fraction. The principal innovations include high-resolution collimation, higher information density, improved method for dynamic aortic-mitral-diaphragmatic border delineation, accurate selection of the end-systolic gating interval through the use of the phonocardiogram, and accurate end-diastole by on-line gating immediately following the electrocardiographic QRS. The results of scintigraphic studies were compared with selective radiopaque cineangiographic findings in 27 patients with cardiac disease; excellent correlations of ejection fractions ($r=0.93$) and abnormal contraction patterns (17/17 patients) were demonstrated. In addition, the clinical usefulness in evaluating ventricular performance was demonstrated in 79 patients with acute and chronic coronary artery disease. This radionuclidic technique allowed assessment of reversibility of segmental dyssynergy by the response to nitroglycerin in 20 patients. These findings demonstrate the validity of this improved radionuclidic technique in the atraumatic quantification of ventricular function and suggest its usefulness in a variety of clinical situations.—*Authors' Abstract*

PEDIATRIC RADIOLOGY

Philip, A. G. S. Oxygen plus pressure plus time: the etiology of bronchopulmonary dysplasia. *Pediatrics*, 1975, *55*, 44. (Address: University of Hawaii, Honolulu, Hawaii.)

Ten infants developed the chronic pulmonary syndrome designated bronchopulmonary dysplasia, following artificial (assisted) ventilation using a volume-regulated positive-pressure respirator. Despite previous reports implicating elevated oxygen concentrations for prolonged periods of time, only two infants required more than 80 percent oxygen for more than 24 hours, and only one infant required 60 percent oxygen for more than 100 hours. "Immature" lungs when exposed to inspired oxygen concentrations over 40 percent for as little as three days via positive-pressure ventilation may develop bronchopulmonary dysplasia. The role of the underlying disease and the relationship with Wilson-Mikity syndrome remain unclarified.—*Author's Abstract*

Berg, T. J., Pagtakhan, R. D., Reed, M. H., Langston, C., and Chernick, V. Bronchopulmonary dysplasia and lung rupture in hyaline membrane disease: influence of continuous distending pressure. *Pediatrics*, 1975, *55*, 51. (Address: University of Manitoba, Winnipeg, Canada.)

Review of 158 patients with hyaline membrane disease was undertaken. The introduction of artificial ventilation with a positive end-expiratory pressure (IPPB and PEEP) has doubled the prevalence of pneumothorax, pneumomediastinum and interstitial emphysema from 30.7 percent to 39.7 percent. Continuous negative distending pressure during spontaneous ventilation (CNP) was associated with a prevalence of lung rupture similar to that occurring spontaneously (4.8 percent). No patient treated with CNP alone developed bronchopulmonary dysplasia. Patients treated with IPPB with PEEP had a marked decreased prevalence of bronchopulmonary dysplasia (17.2 percent) when compared to patients treated with IPPB alone (36.2 percent), probably related to the enhanced ability to rapidly reduce inspired oxygen concentrations. It is postulated that unequal time constants with subsequent overdistension of relatively normal areas of the lung may explain the increased prevalence of lung rupture seen during IPPB with PEEP.—*Authors' Abstract*

GOETZMAN, B. W., STADALNIK, R. C., BOGREN, H. G., BLANKENSHIP, W. J., IKEDA, R. M., and THAYER J. Thrombotic complications of umbilical artery catheters: a clinical and radiographic study. *Pediatrics*, 1975, *56*, 374–379. (From: University of California, Davis, California.)

Catheterization of the aorta via the umbilical artery provides a convenient route for monitoring arterial blood pressure, for obtaining blood specimens for measurement of blood gas tensions and chemistries, and for the infusion of fluids and pharmacologic preparations in sick newborn infants. Use of this technique may be accompanied by a number of complications of which thrombotic phenomena are the most common. Twenty-three of 98 (24 percent) newborn infants undergoing umbilical artery catheterization were found to have thrombotic complications determined by aortography. No correlation was present between the duration of time that the umbilical artery catheters were in place and the occurrence of thrombotic complications. From paired aortographic or aortographic and autopsy studies in 24 patients, it was concluded that if a thrombotic complication did not occur early, none was likely to occur subsequently. One patient was considered to have died as a direct result of a thrombotic complication. Aortography is a safe, simple, and reliable technique for the early detection of thrombotic complications of umbilical artery catheters. Umbilical artery catheterization is not without risk and careful selection of patients for this procedure is emphasized.—*Authors' Abstract*

BERGESON, P. S., HALES, S. W., LUSTGARTEN, M. D., and LIPOW, H. W. Pneumatoceles following hydrocarbon ingestion: report of three cases and review of literature. *Am. J. Dis. Child.*, January, 1975, *129*. (Address: Good Samaritan Hospital, 1033 East McDowell Road, Phoenix, Arizona 85006.)

Three cases of pneumatocele formation secondary to hydrocarbon ingestion are reported and analyzed along with 12 from the literature. The cases display a spectrum of clinical severity. After a period of 3 to 15 days, during which most patients became asymptomatic, pneumatoceles were noted radiologically, usually as an unexpected finding on follow-up roentgenograms. No instances of pneumothorax or empyema were noted. Resolution has been observed radiologically after periods varying from 15 days to 21 months.—*Authors' Abstract*

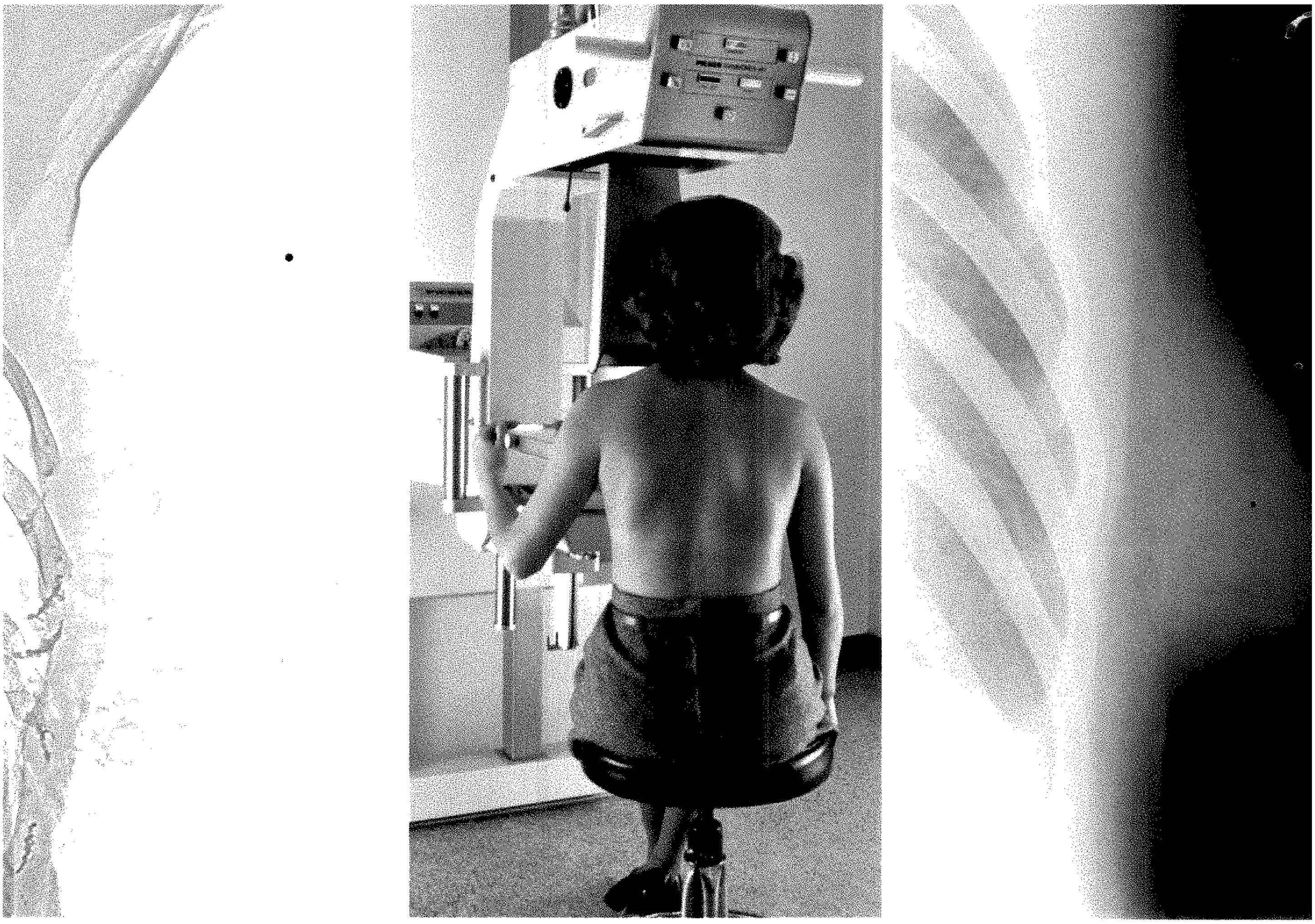
GREENE, W., L'HEUREUX, P., and HUNT, C. E. Paralysis of the diaphragm. *Am. J. Dis. Child.*, 1975, *129*, 1402–1405. (Address: Dr. Hunt, 2300 Children's Memorial Hospital Plaza, Chicago, Illinois 60614.)

Diaphragmatic paralysis has been mentioned infrequently as a cause of respiratory symptoms in children. During a three year period, diaphragmatic paralysis has occurred in 12 neonates following birth trauma (six) or thoracotomy (six) and in four older children following thoracotomy.

Spontaneous recovery occurred in all four older children and in five of the 12 neonates. Although two neonates became asymptomatic despite persistent paralysis, the remaining five neonates required prolonged intermittent positive-pressure breathing; two eventually died of secondary pneumonia, and three became asymptomatic only after plication of the affected diaphragm was performed.—*Authors' Abstract*

SANTULLI, T. V., SCHULLINGER, J. N., HEIRD, W. C., GONGAWARE, R. D., WIGGER, J., BARLOW, B., BLANC, W. A., and BERDON, W. E. Acute necrotizing enterocolitis in infancy: a review of 64 cases. *Pediatrics*, 1975, *55*, 376. (Address: The Children's Medical and Surgical Center, Columbia-Presbyterian Medical Center, New York, New York.)

Sixty-four cases of necrotizing enterocolitis are reviewed. The diagnosis was based on tissue examination in 57 and on the clinical syndrome, including pneumatosis, in 7. Three factors are important in the development of the disease: injury to the intestinal mucosa, bacteria, and feedings. The indications for surgical intervention are pneumoperitoneum, signs of peritonitis, and intestinal obstruction. The importance of stress in the etiology of the disease is confirmed by the high incidence of perinatal complications, particularly hypoxia. The mortality was high, but results are improving with the institution of early aggressive treatment.—*Authors' Abstract*



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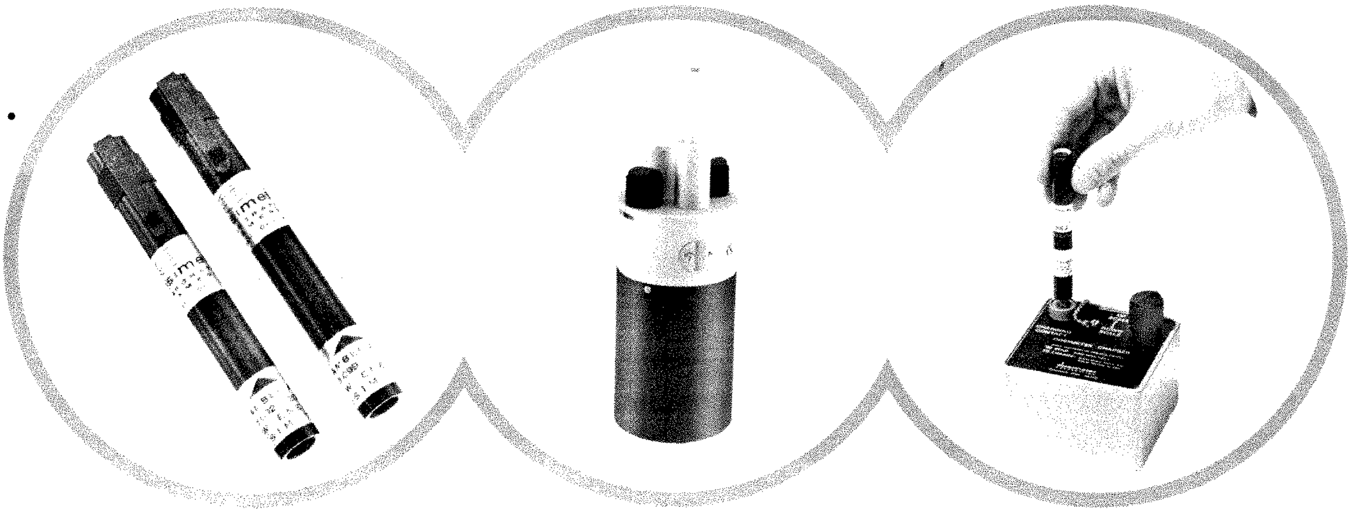

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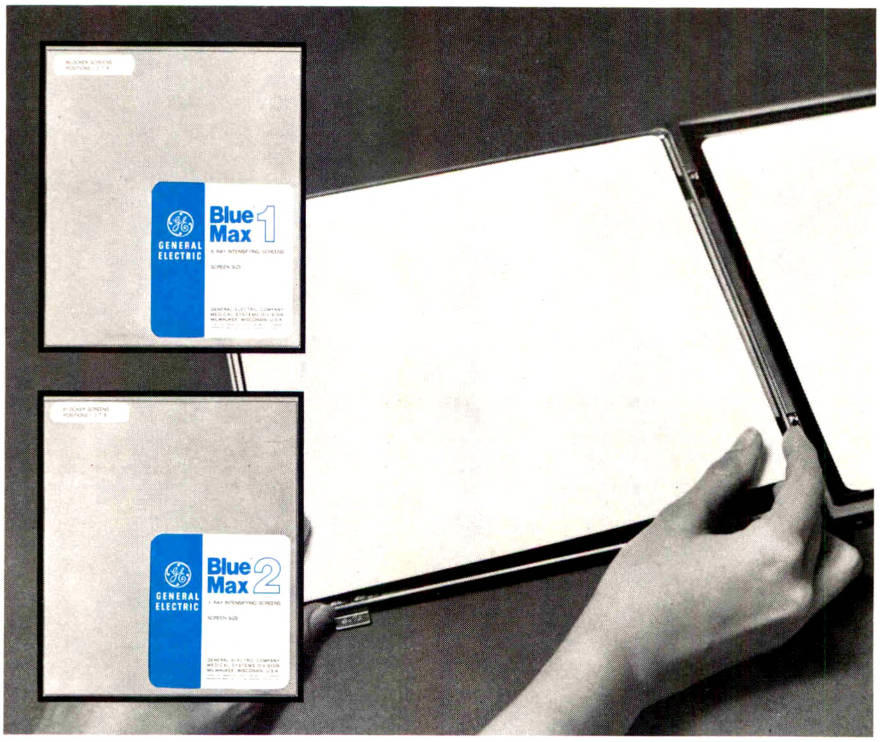

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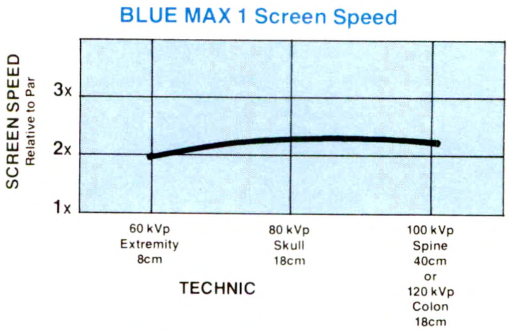
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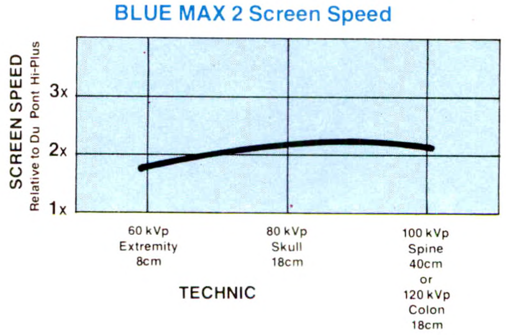
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MAY 19, 20, 21, 1976

At the Bayshore Inn (Western International Hotels), Vancouver

PROGRAM

Wednesday, May 19

Morning *Chest*

—Pulmonary Edema .... Robert G. Fraser.
—Diffuse Bilateral Pulmonary Disease in Children .... J. Scott Dunbar.
—Pleuropulmonary Changes in Non-penetrating Thoracic Trauma .... John G. Clement.
—Immunological Diseases of the Thorax .. Robert G. Fraser.
—Cyst and Cyst-like Lesions of the Lung in Children .... J. Scott Dunbar.

Afternoon *Skeletal*

—Iatrogenic Lesions of the Skeleton .... Ronald O. Murray.
—Some Interesting Aspect of Skeletal Trauma .... Harold G. Jacobson.
—Importance of Soft Tissue in Relation to Skeletal Radiology .... Ronald O. Murray.
—The Hand as a Mirror of Local and Systemic Diseases .... Harold G. Jacobson.

Film Reading Session:

Chairman: Harold G. Jacobson
Panelists: J. Scott Dunbar, Robert G. Fraser, Ronald O. Murray.

Thursday, May 20

Practical Techniques in Diagnostic Radiology

Morning

—Gastrointestinal Examination in Infants and Children .... J. Scott Dunbar.
—Non-Operative Removal of Common Duct Stones .... H. Joachim Burhenne.
—Angiographic Techniques in Control of Gastrointestinal Hemorrhage .... Josef Rösch.
—Peritoneography: Normal & Pathological Anatomy .... Morton A. Meyers.
—Genitourinary Examination in Neonates and Infants .... Walter E. Berdon.
—PANEL DISCUSSION.

Afternoon

—Techniques and Advances in Myelography .... Alan J. Fox.
—Percutaneous Biopsy of Lung, Kidney and Bone .... Anthony F. Lalli.
—Chest Radiography .... Robert G. Fraser.
—Equipment and Techniques in Abdominal and Obstetrical Ultrasound .... George R. Leopold.
—PANEL DISCUSSION.

Friday, May 21

Morning *Gastrointestinal Radiology*

—Diagnosis of Gallstones .... H. Joachim Burhenne.
—Seeded Metastases: Pathways and Diagnostic Features .... Morton A. Meyers.
—Abdominal (non-obstetrical) Ultrasonography .... George R. Leopold.
—Angiography of the Liver & Pancreas .... Josef Rösch.
—Anatomy of the Post-Op. Stomach .. H. Joachim Burhenne.
—Intestinal Effects of Pancreatitis ...... Morton A. Meyers.

Afternoon *Genitourinary Radiology*

—Controversies on Reflux, Infection and Pyelonephritic Scarring .... Walter E. Berdon.
—Renal Papillary Necrosis .... Anthony F. Lalli.
—Renal & Adrenal Angiography .... Josef Rösch.
—Obstetrical Ultrasonography .... George R. Leopold.
—Obstructive Uropathies .... Walter E. Berdon.
—Calculi and Calcifications of the Urinary Tract .... Anthony F. Lalli.

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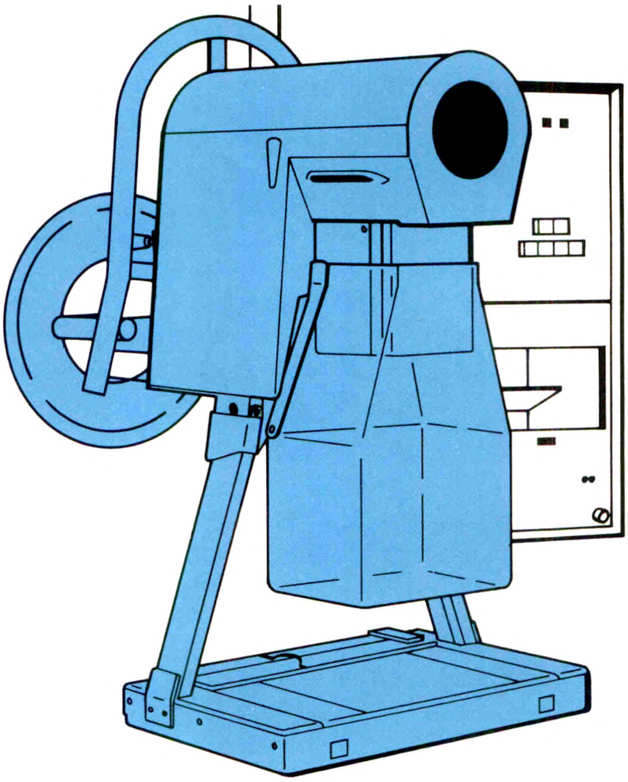

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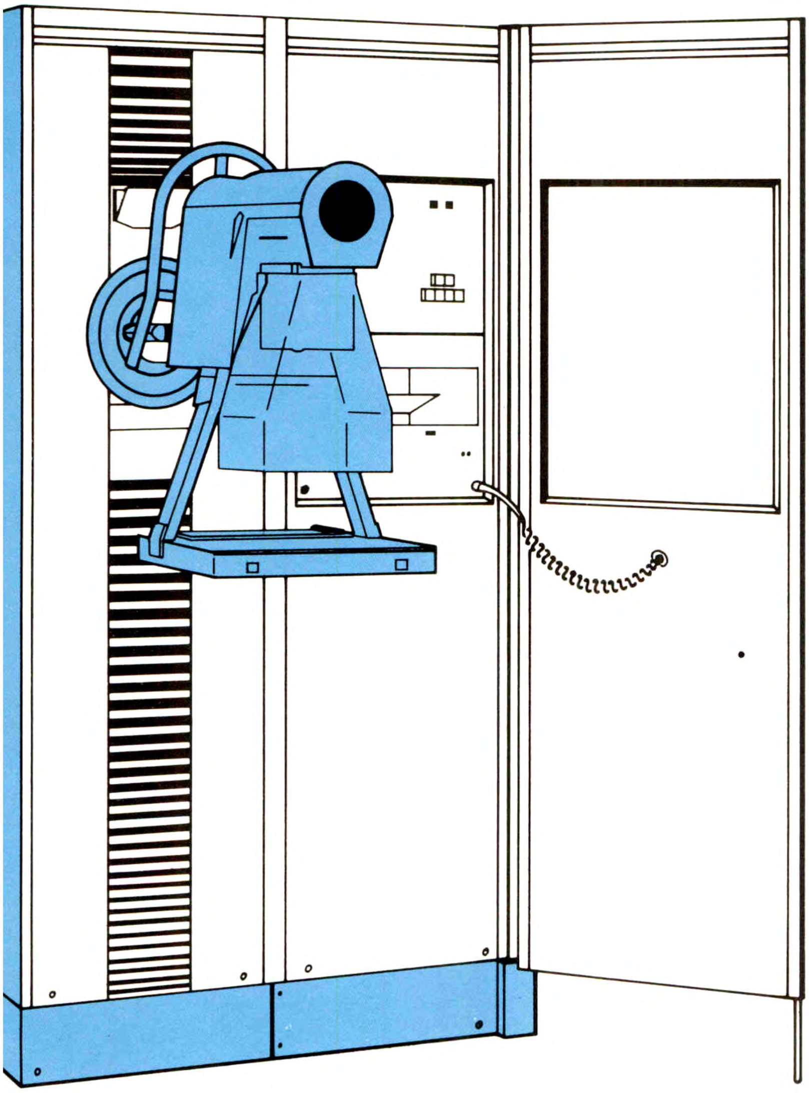

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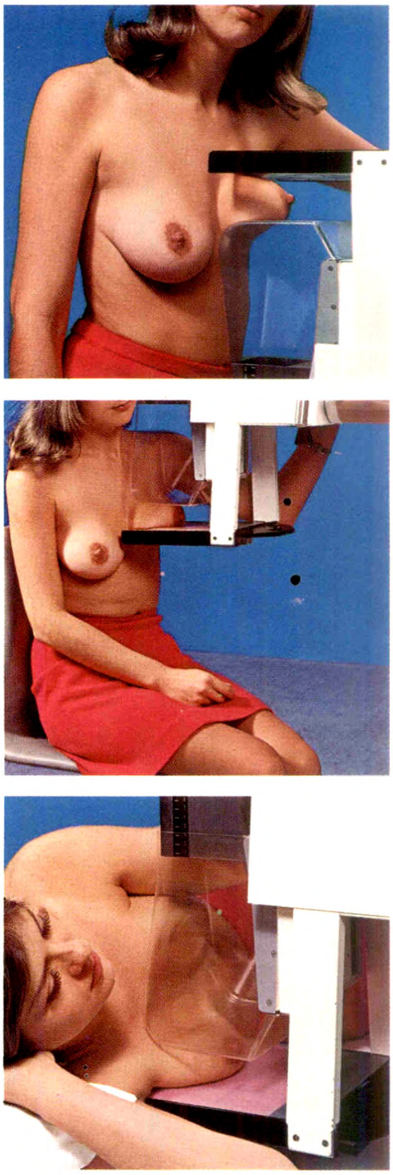

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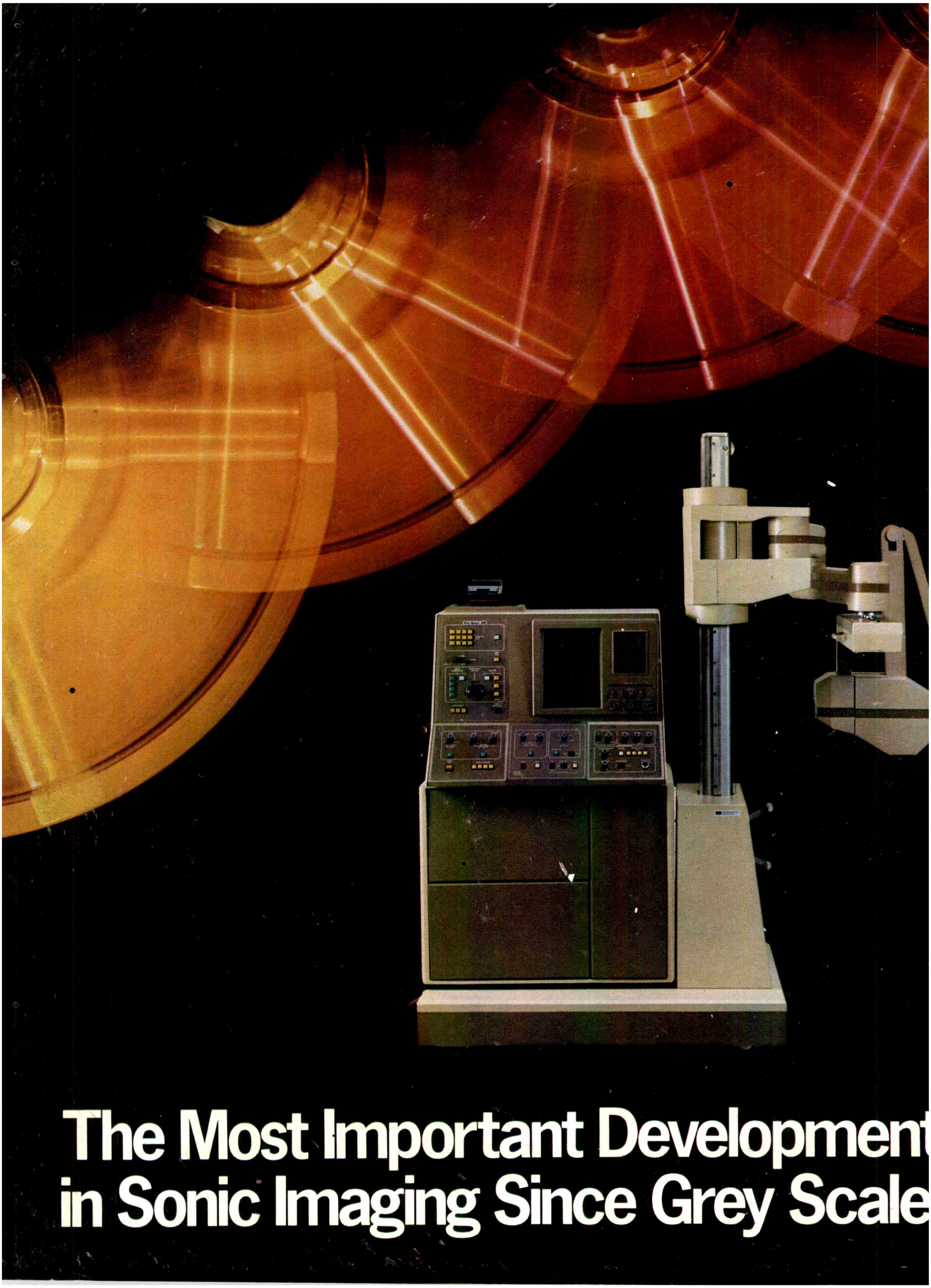
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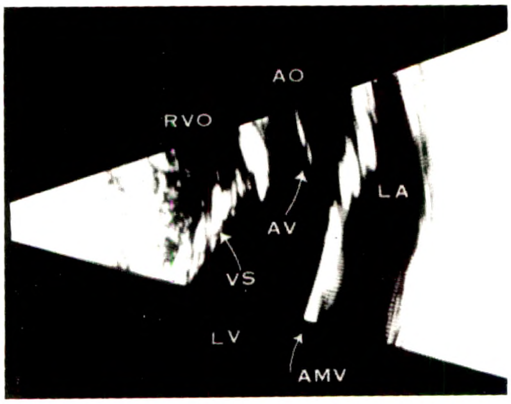

*Fig. 14-23. Stop-action image of a normal patient made with a real time motorized sector scanner. This device rapidly scans a single crystal through a sector angle of 37.5° and provides a real time motion image of the heart in two dimensions. Movement of an entire structure such as the anterior mitral valve and the aortic valve can be readily viewed. Single frame studies are available for quantitative image analysis.

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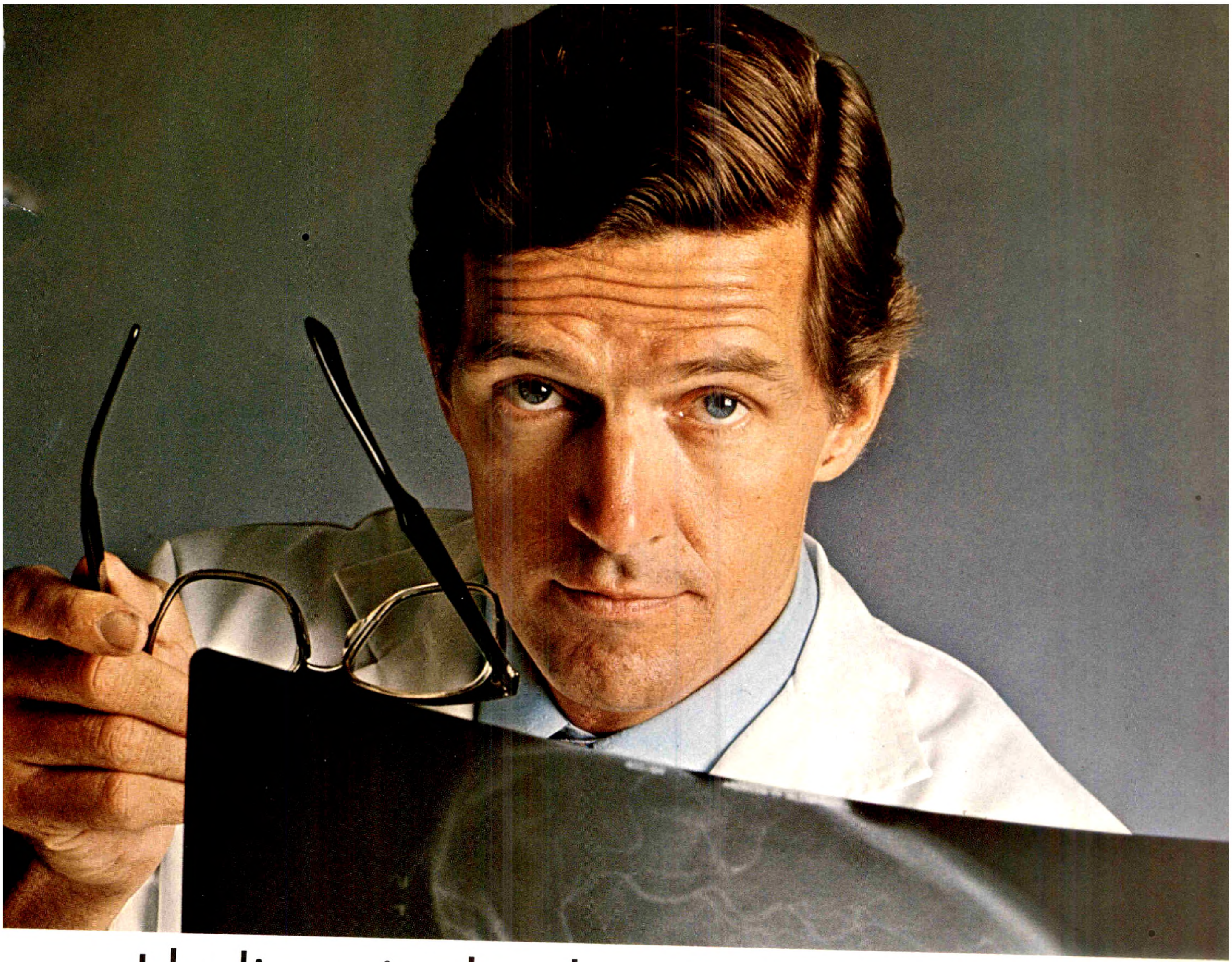

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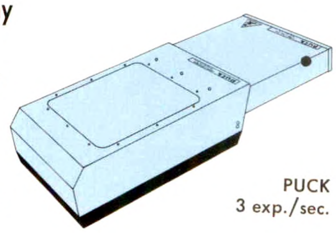

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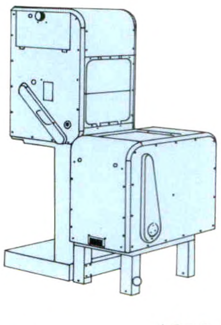

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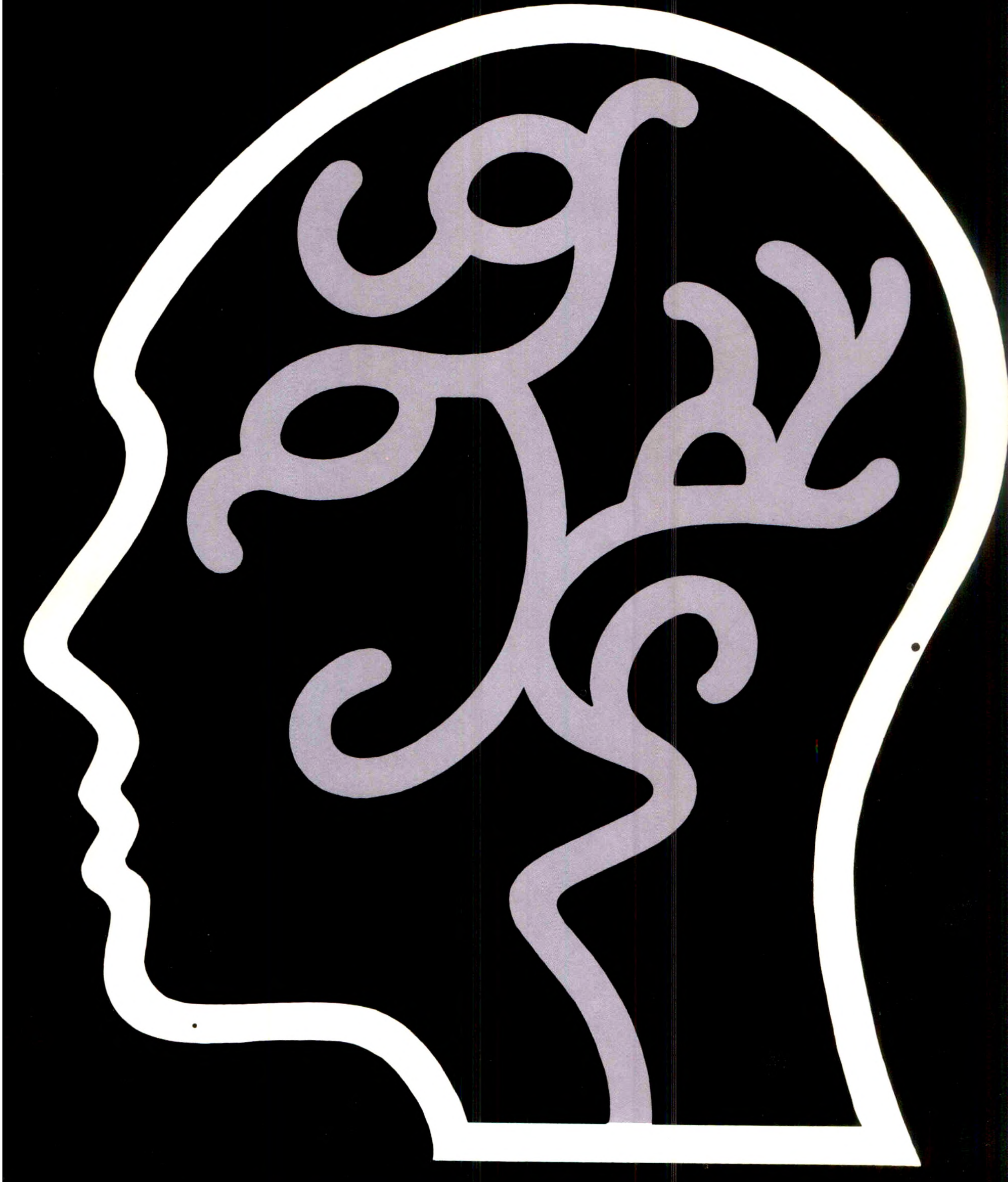

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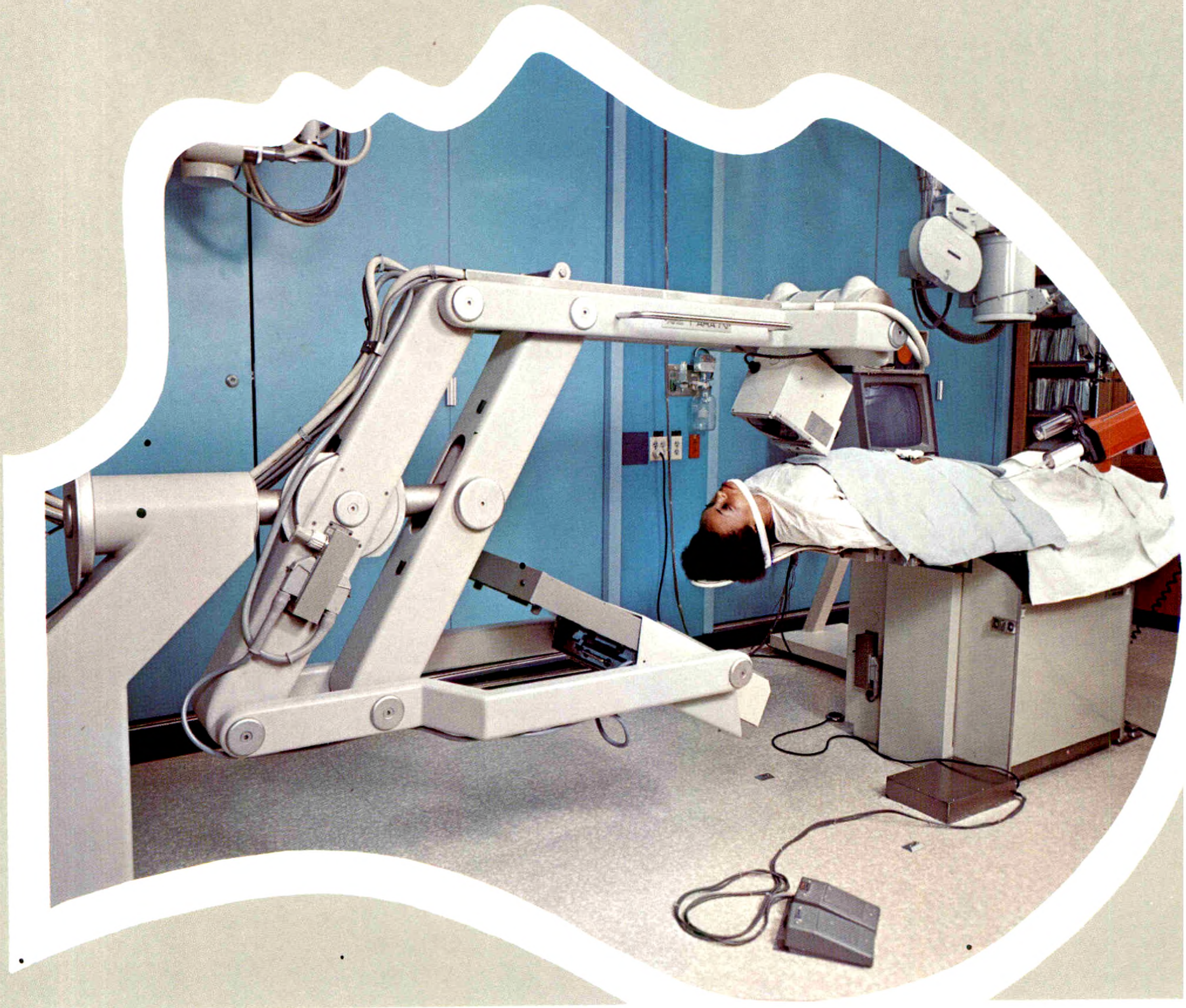

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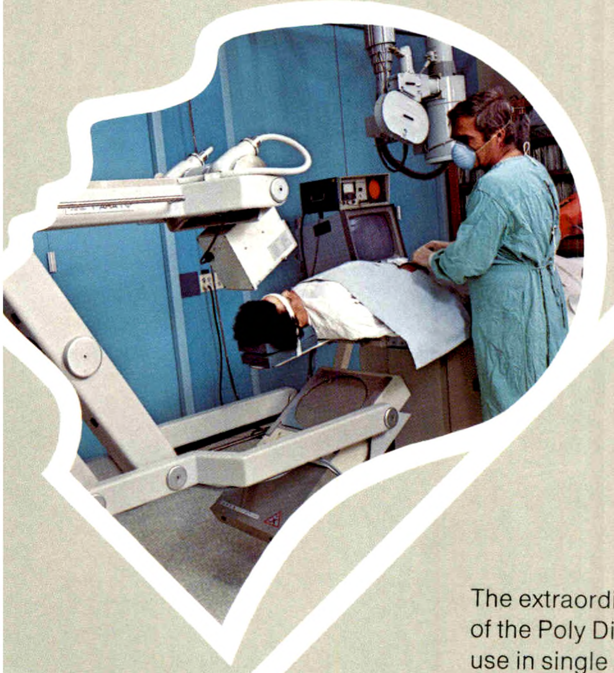

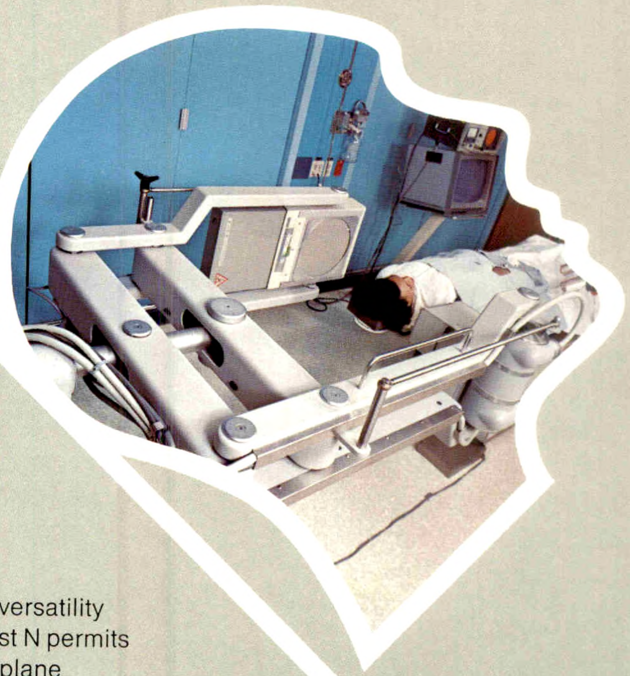

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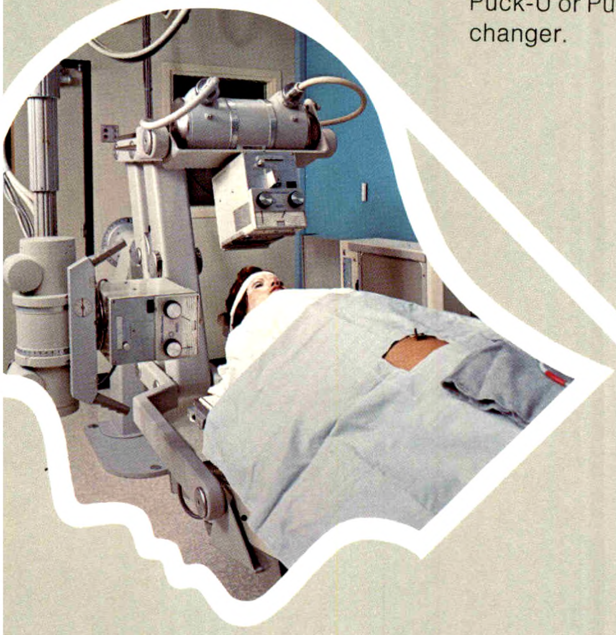

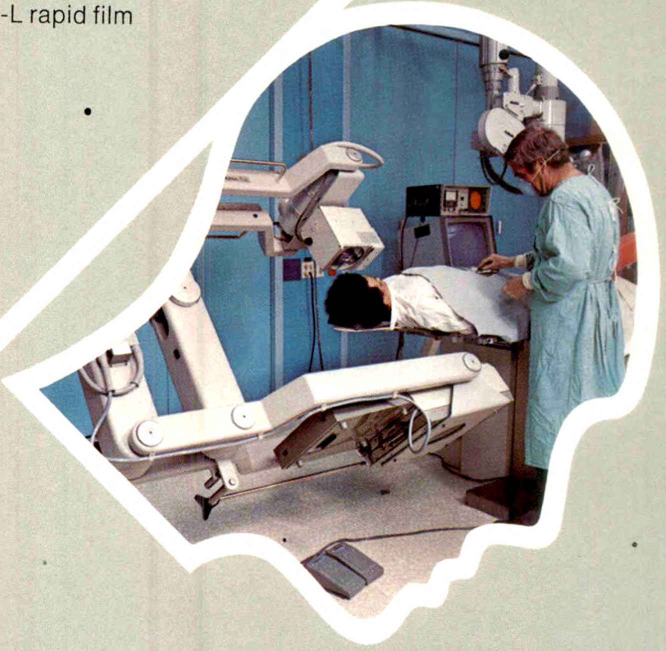

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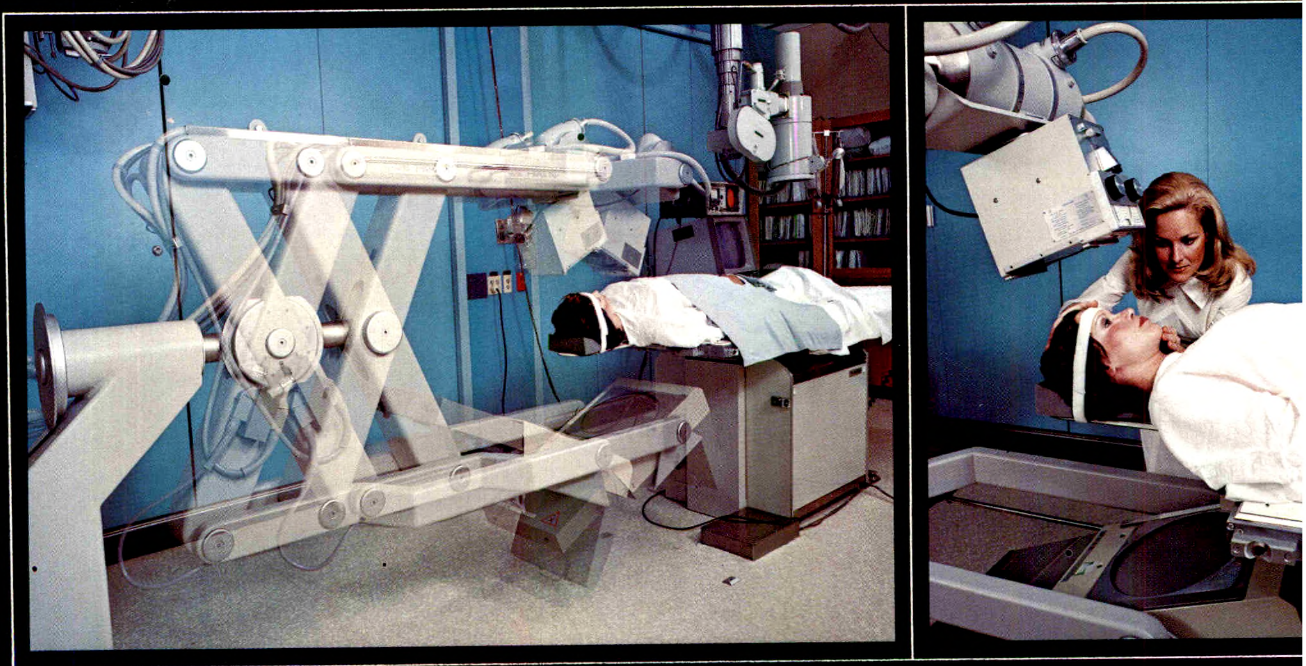

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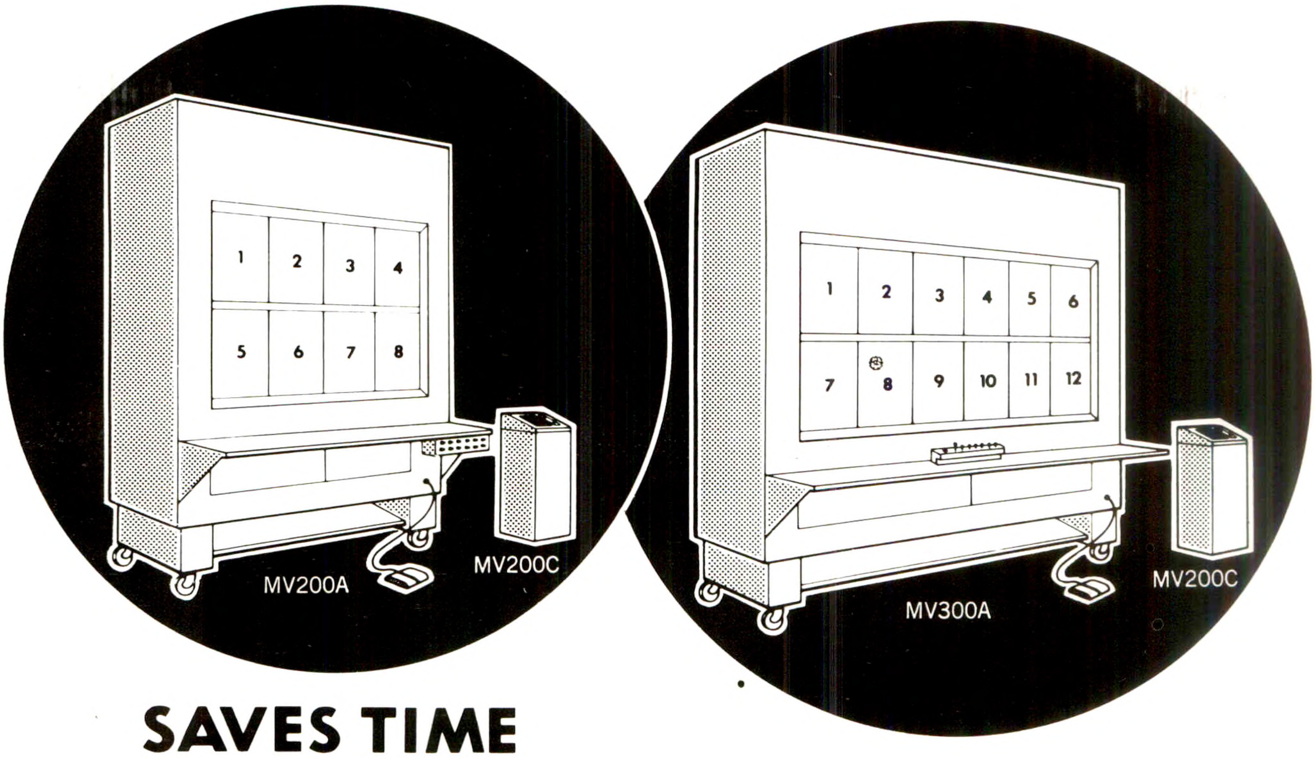

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Quanta II screens are fully compatible with the Du Pont family of quality films as well as all other conventional films. There is no need to purchase special films to realize increased speed.

Because of this compatibility, you can now have a wide selection of system speeds and be assured of maximum convenience and flexibility in meeting your imaging requirements. Here are just a few of the film/screen combinations now availab

Imaging Requirement	Film/Screen	Results
High Speed	Cronex® 4/Quanta II	Twice the speed of Cronex® 4/Hi-Plus Excellent diagnost clarity.
Improved Diagnostic Clarity at Conventional Speed	Cronex® 7/Quanta II	Low Haze. Low noi Clarity like Cronex 2DC but with 90-second processin Speed equal to Cronex® 4/Hi-Plu
High Speed with Excellent Visualization of Bone Detail and Soft Tissue	Cronex® 6 Plus/ Quanta II	Superb low-densit contrast. Extende recording range. Twice the speed o Cronex® 4/Hi-Plu

can increase system speeds diagnostic clarity.

Excellent Diagnostic Clarity

Quanta II screens provide diagnostic clarity similar to Cronex® Hi-Plus. The increased speed means there is less chance of blurred images caused by patient motion. In addition, since smaller focal spots can be used, Quanta II is ideal for specialized procedures such as magnification angiography.

Lower Operating Costs

Quanta II screens are reasonably priced and can help reduce operating costs in Radiology Departments. Their increased speed means less tube load so that X-ray equipment will last longer. You can even consider lower-powered, less costly generators. And, because Quanta II screens are blue-emitting, no special safelights are required.

To learn more about these new high-speed, blue-emitting screens, ask your Du Pont Technical Representative for a free demonstration of Quanta II—today's screen for tomorrow's needs.

Or, write Du Pont Company, Room 24784, Wilmington, Delaware 19898.

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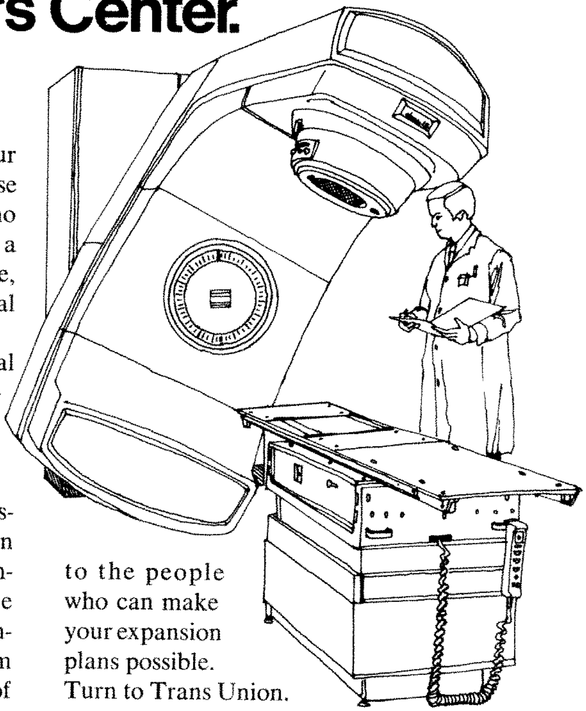

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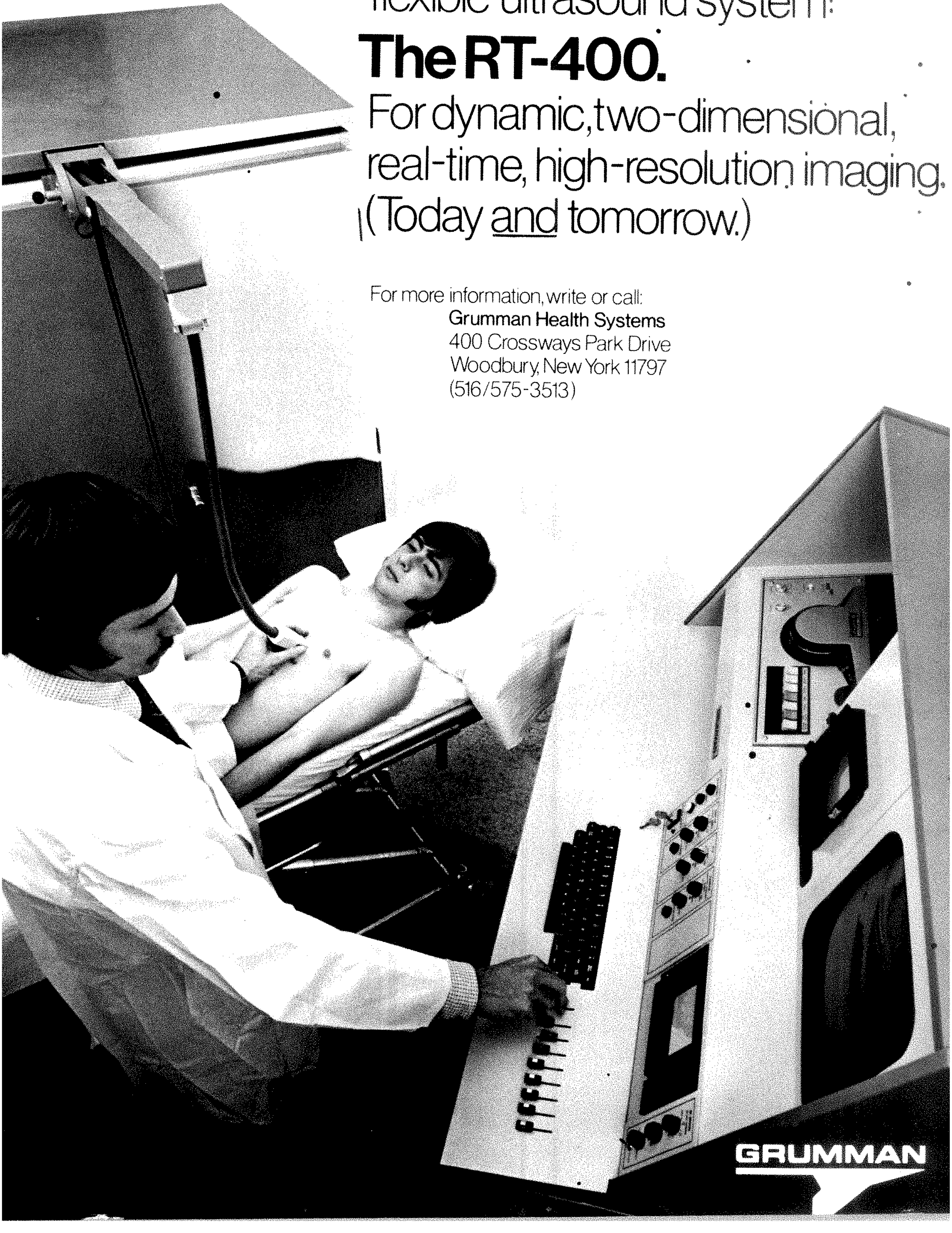

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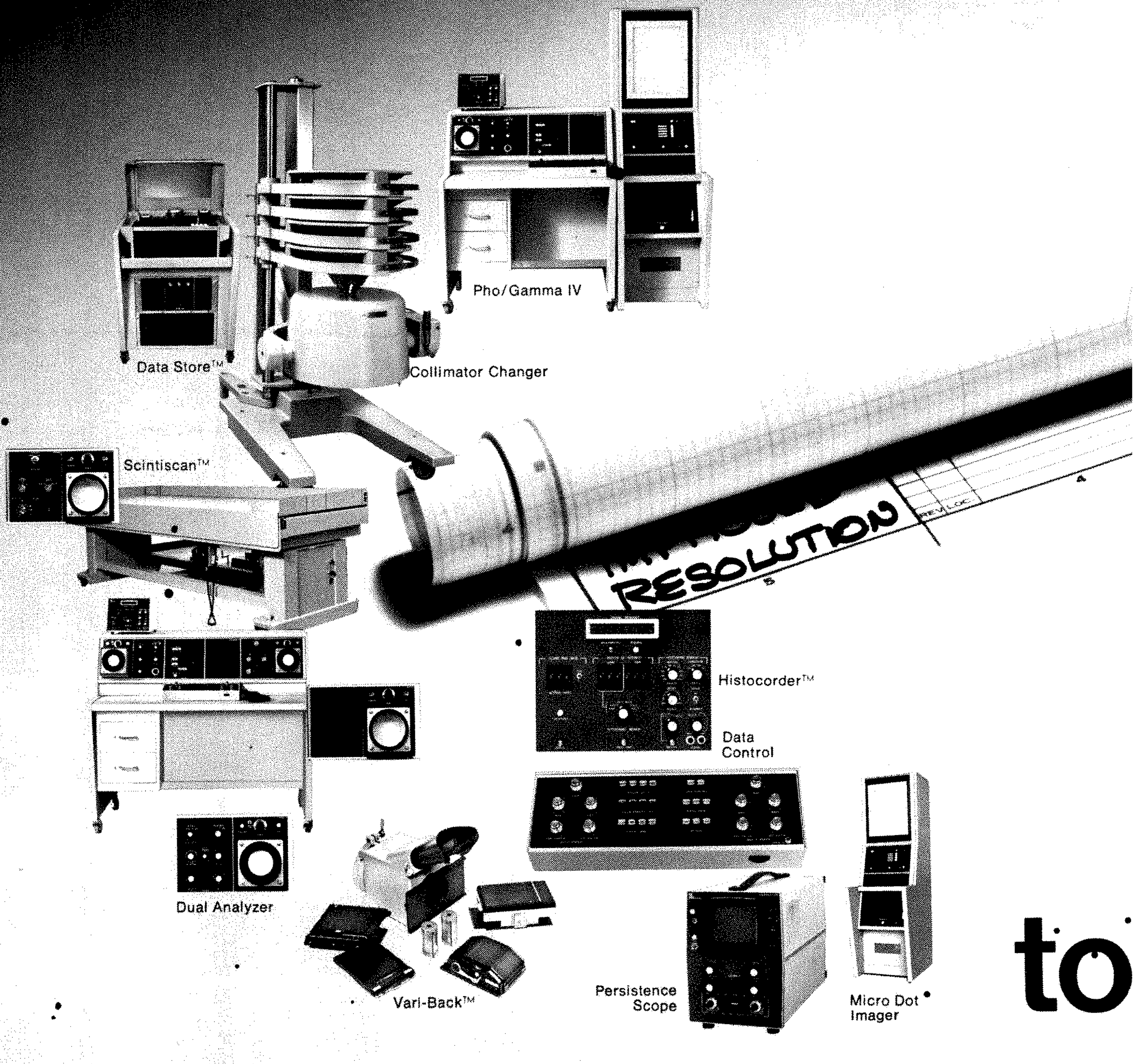

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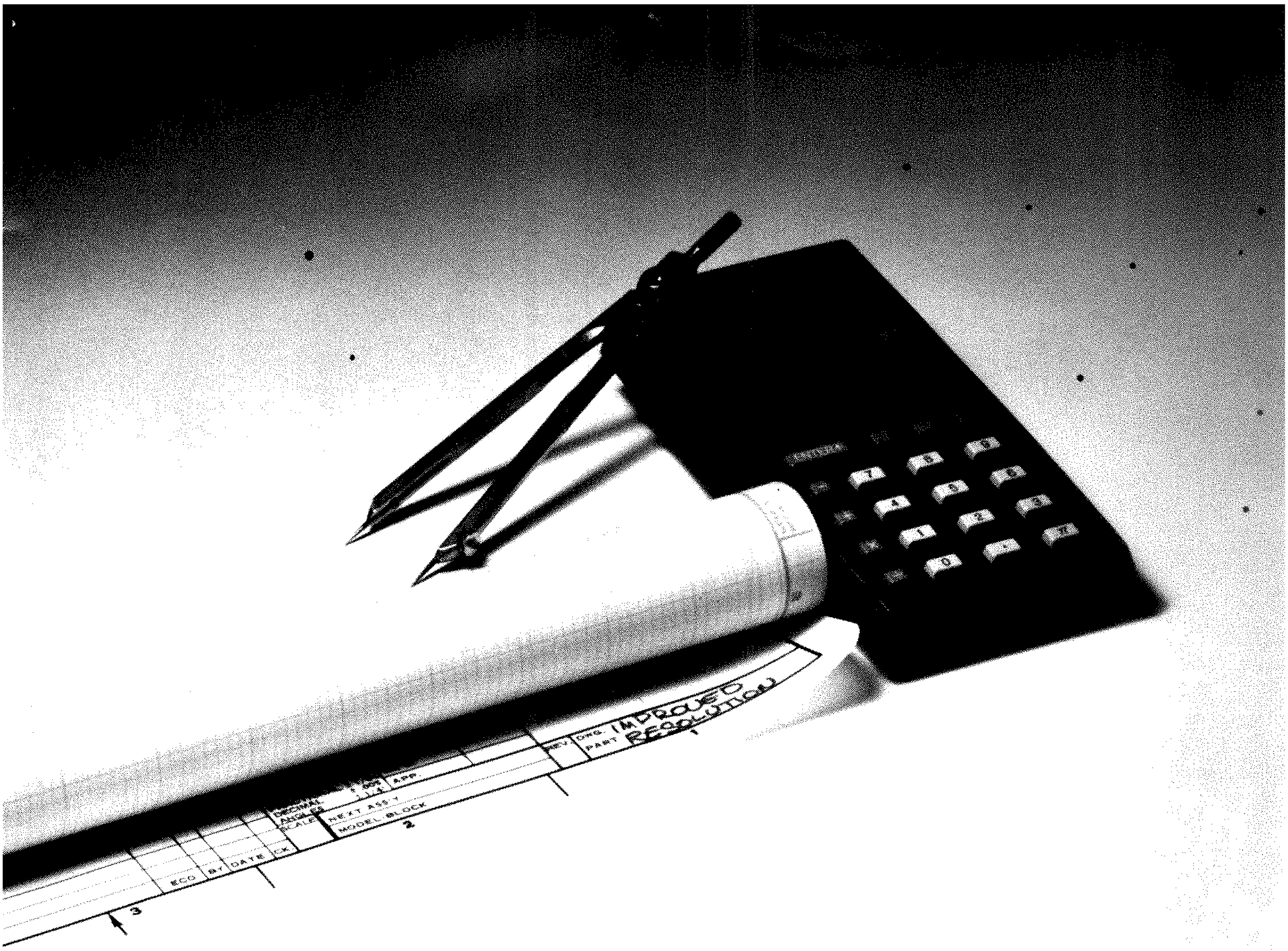

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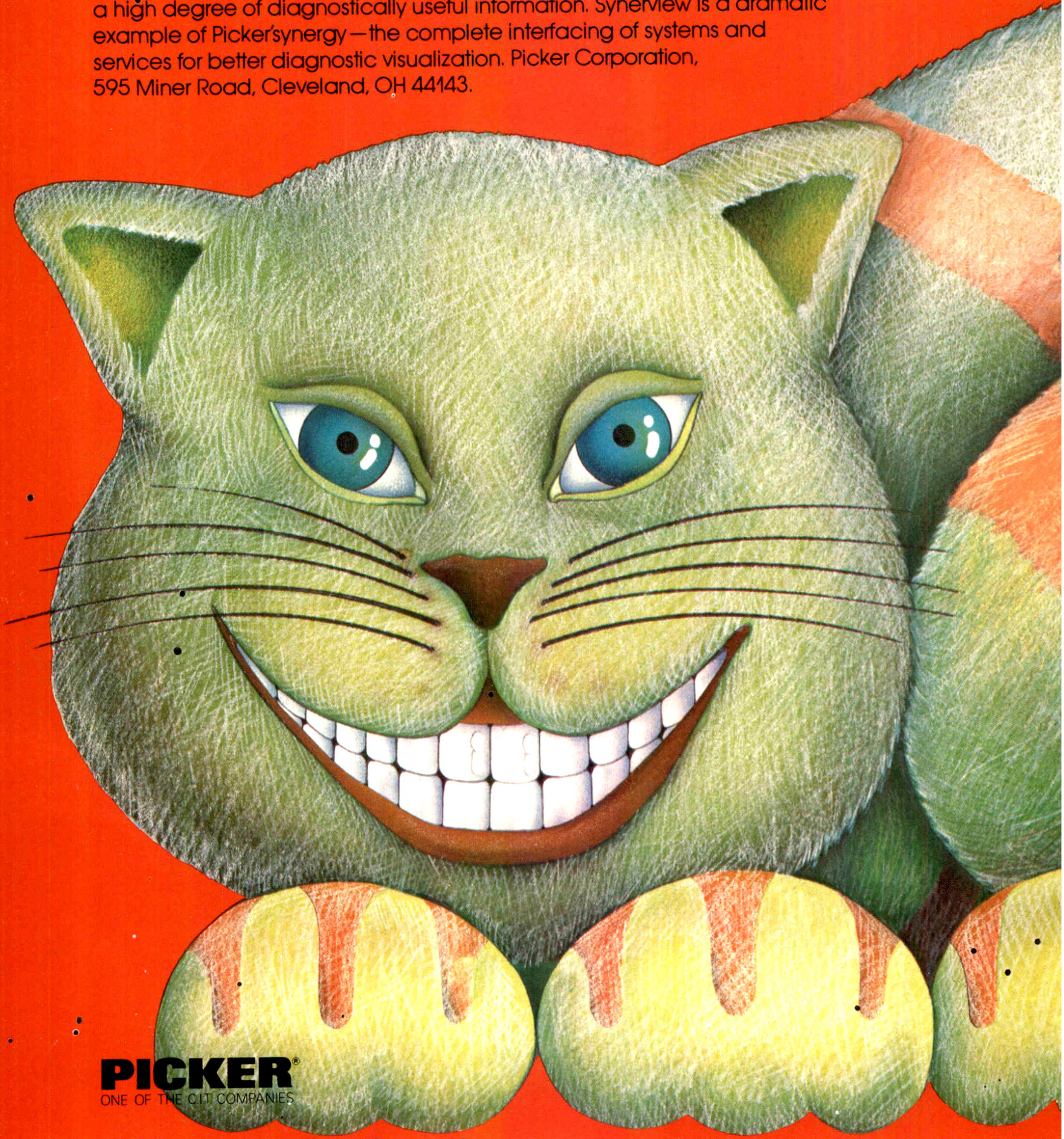

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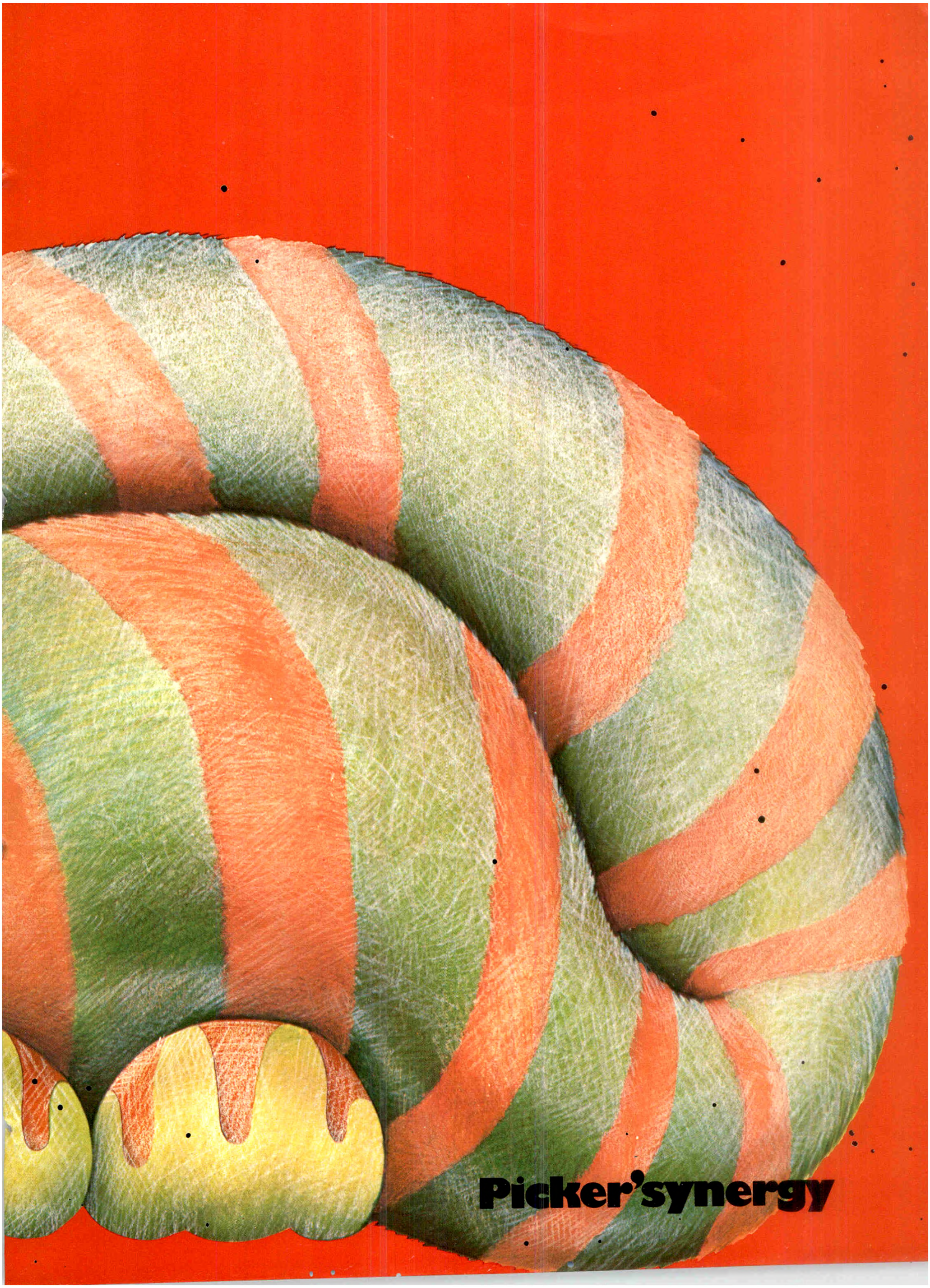
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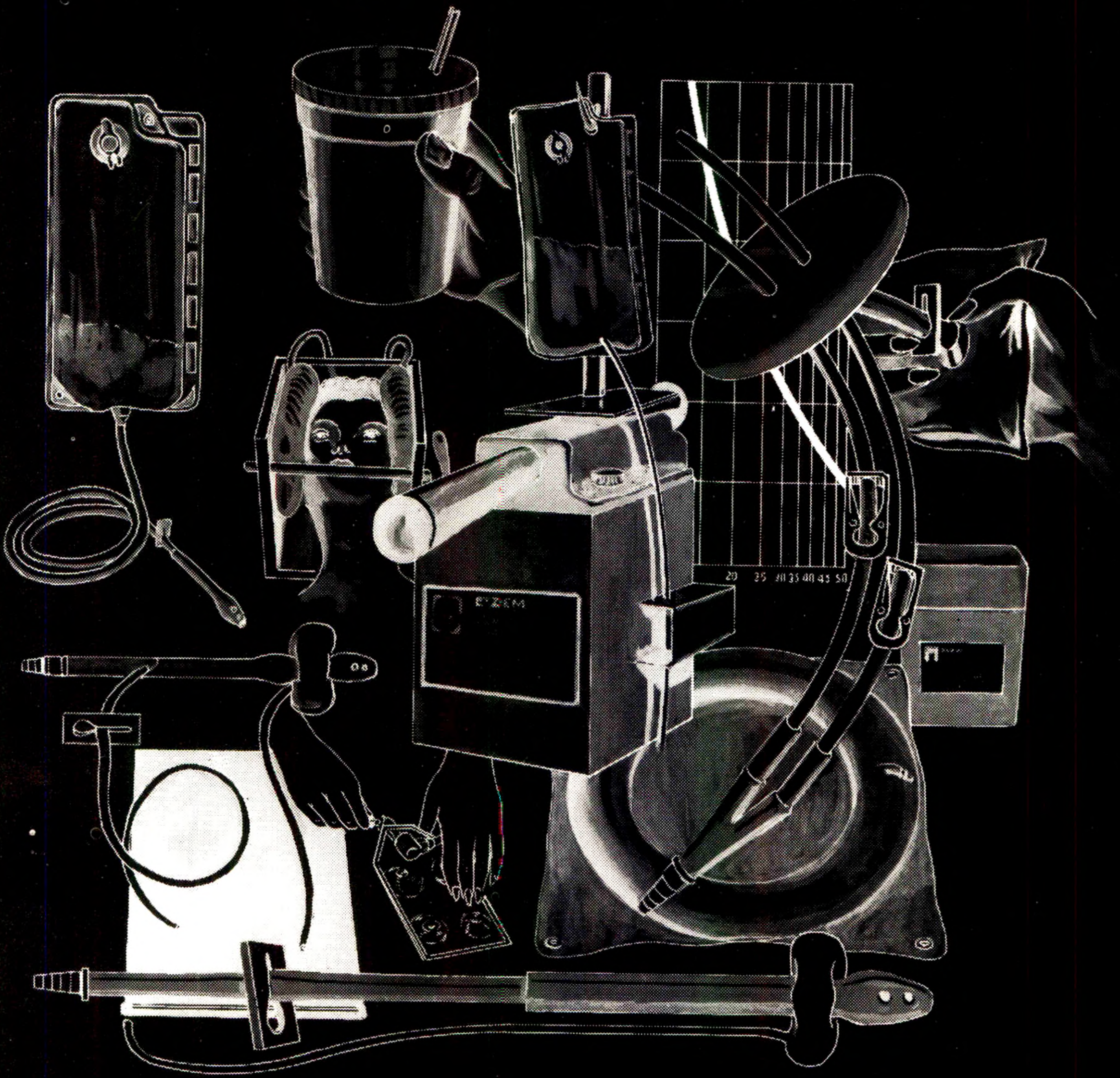

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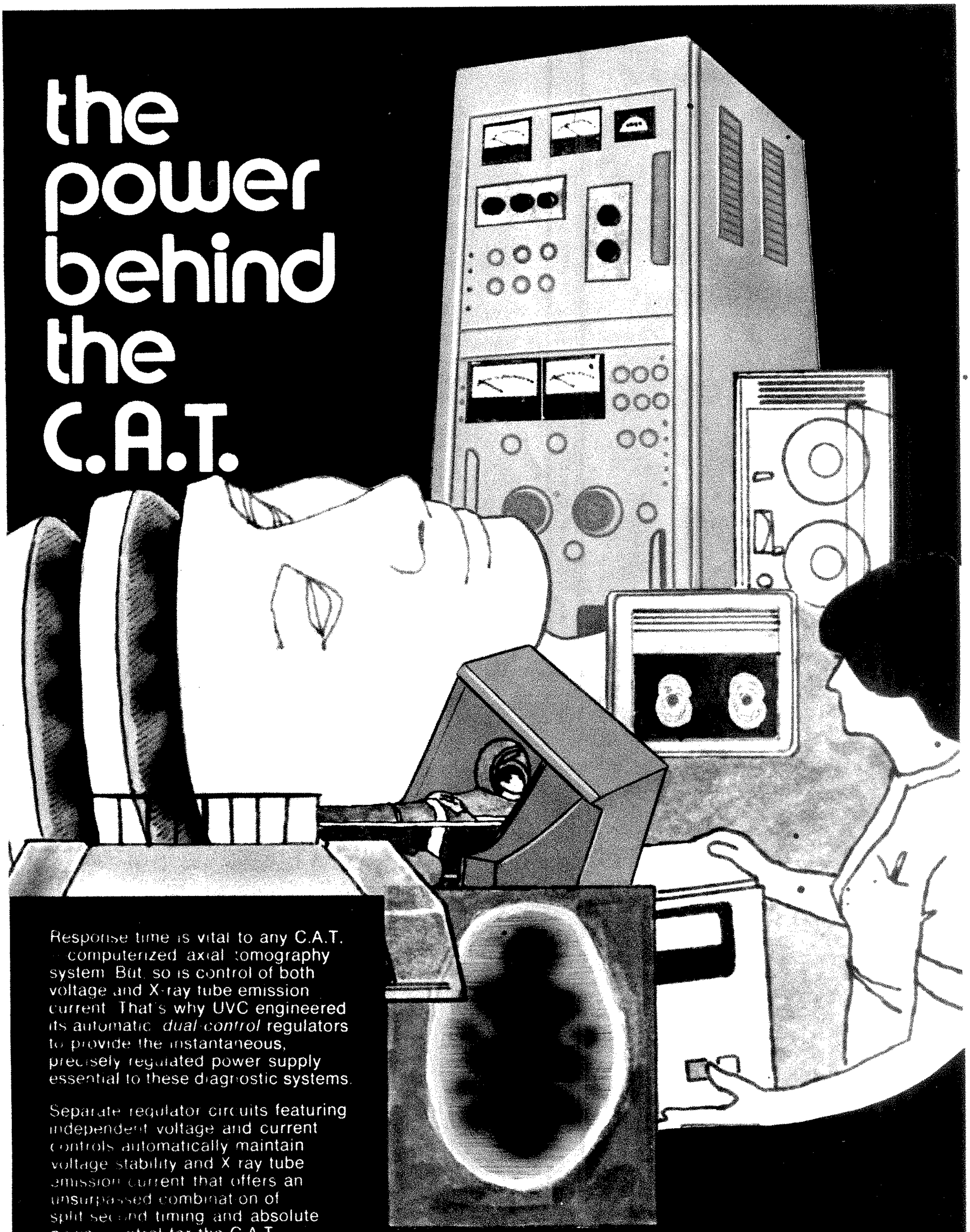
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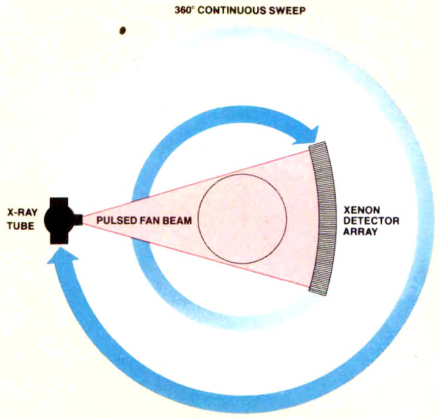
GE research solves the primary problem of existing total body scanners—motion unsharpness.

GE fast-scan computerized tomography: a whole new generation.



Third generation: GE's continuously rotating pulsed fan beam scanning. 5 to 10 seconds.

First and second generation units aren't fast enough for total body scanning.

First and second generation computerized tomography systems have one major problem: image blurring caused by patient movement during body scans.

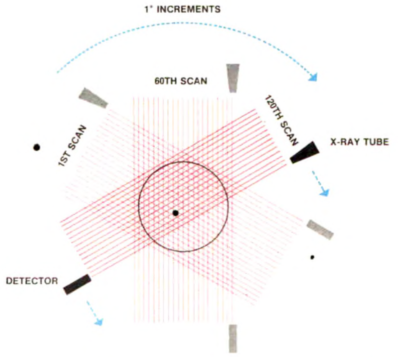
General Electric research has developed a fast-scan technology that is launching a new third generation of computerized tomography (CT) systems. The faster scans provide clear, sharp images.

During body studies, patient movement caused by breathing can result in motion unsharpness.

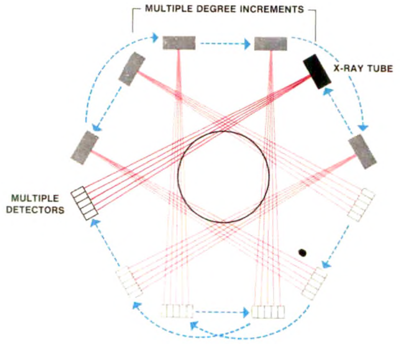
To really tackle this problem, a scan should take less time than a patient can hold his breath comfortably—10 seconds or less. However, existing computerized tomography systems cannot match this speed.

First generation units, using a pencil beam with a 1° incremental rotate-and-translate principle, take 4½ to 5½ minutes to complete a 180° scan.

Second generation systems use multiple pencil beams and more detectors—up to 30. Rotation is in larger angular increments. This configuration takes from 20 seconds to 3½ minutes per scan.



First generation: Pencil beam rectilinear scanning. 4½ to 5½ minutes.



Second generation: Multiple pencil beam rectilinear scanning. 20 seconds to 3½ minutes.

GE develops continuously rotating fan beam technology for fast-scan capability.

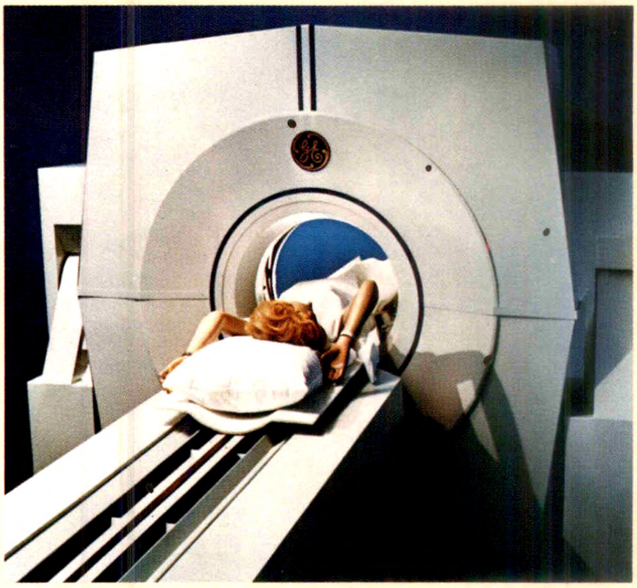
In developing an entirely new total body system, GE engineers and scientists abandoned the incremental rotate-and-translate approach of first and second generation units, with their inherent mechanical instability and resultant speed limitations. Instead, GE used a simpler, more stable mechanical approach, in which the tube and detectors rotate smoothly about the body in a continuous 360° scan, without need for translation.

This new third generation technology combines a continuously rotating, pulsed, wide fan x-ray beam with a unique high-pressure xenon detector array of up to 320 stable detectors. Advanced electronics are included to read out the huge volume of data. And GE has successfully conceived and implemented a new computational approach compatible with diverging fan beam geometry.

Third generation fast-scan technology proven on CT/M system.

GE's first application of fast-scan technology utilized computerized tomography's tissue density differentiation capability in the challenging area of breast examinations. This unit, called the CT/M system, is currently being clinically evaluated. Scans are completed in just 10 seconds. Patient handling is minimized. If you are interested in further information about the CT/M system, contact your GE representative or write for Publication 4675.

CT/M System



CT/T System

CT/T system performs body scans in less than 5 seconds.

The CT/T system for total body scanning is moving into the clinical environment. Scan time for the CT/T unit is 4.8 seconds. GE engineers believe this unprecedented scanning speed will provide consistently sharp, clear images for body studies. First production units are scheduled for the last half of 1976. The new CT/T systems represent the culmination of one of General Electric's most extensive research and development programs.

There's a corporate commitment behind GE scanning equipment.

All General Electric scanning systems are backed by the same company that has been serving radiology since the revolutionary Coolidge x-ray tube was introduced 63 years ago. And that kind of corporate dedication to excellence in medical equipment continues today . . . with the development of continuously rotating, pulsed fan beam technology.

As you consider CT scanning equipment, remember GE's continuous commitment to technology, product quality and service. That commitment is an important part of every GE medical system.

Fast-scan CT: backed by GE.

GENERAL ELECTRIC

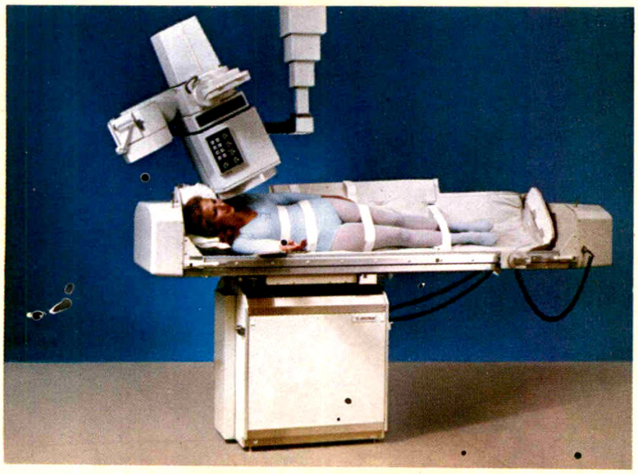
General Electric continues its commitment to the total radiology department.

GE: innovation through technology.

General Electric's extensive CT scanning development program represents only part of a total technological commitment to radiology. As the nation's leading manufacturer of x-ray equipment, GE is pledged to meeting the total needs of radiology departments. A continuing investment in research has resulted in new ideas and product innovations that solve day-to-day departmental problems. Here are some examples:

How to give one procedures room the capability of two.

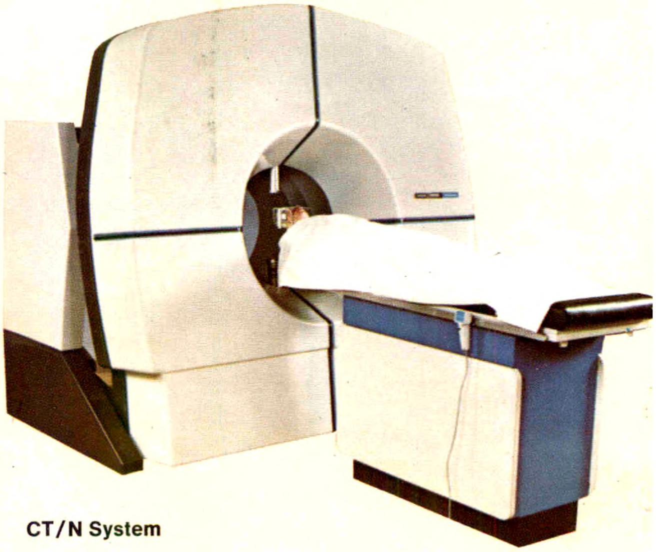
The LAD system adds the capability of a dedicated coronary procedures room to a classical vascular room, permitting all angiographic procedures. Even the axial projection of the left anterior descending coronary artery is obtainable with the LAD system. The unique design features an angulating tube and intensifier with detachable linkage, combined with a rotating patient cradle. Radiation is minimized, with the primary beam shielded by a lead-lined table base. You get Fluoricon® 300 image quality, excellent rigidity and positioning ease. The LAD system: total angiographic capability at minimum cost.



LAD System

When to use first and second generation CT scanners.

The slower scan times of first and second generation CT systems are acceptable for studies of the head. Here, the anatomy can be immobilized, reducing motion unsharpness.



CT/N System

High quality image performance is provided at a moderate cost. For departments where economics and/or volume indicate a need for this type of scanner, GE offers the CT/N system . . . a dedicated neuro unit. Both first and second generation CT/N systems are available, with scan times of 4½ and 2 minutes, respectively. All CT/N systems feature Individual Patient Discs, which serve as a permanent patient record. These discs store up to eight tomographic scans which can be reconstructed and manipulated at the control console or a viewing unit at any time.

Telegem 90 System

How to get your new R&F room installed in 3 weeks or less.

"Pre-staging" is a new service now being offered by General Electric. *Before* your new pre-staged system leaves our plant, it is completely set up and checked out. All components are assembled, all wiring is checked and all mechanical and electrical functions are tested. We make sure your system is completely operational before it's installed in your department. Pre-staging is available on all GE "preferred" vascular and R&F systems, including Televix™ and Telegem® remote systems. Most pre-staged systems can be fully installed in the hospital in just three weeks or less, from start to finish, minimizing departmental downtime, maximizing patient throughput.

How to give your tube unit solid support.

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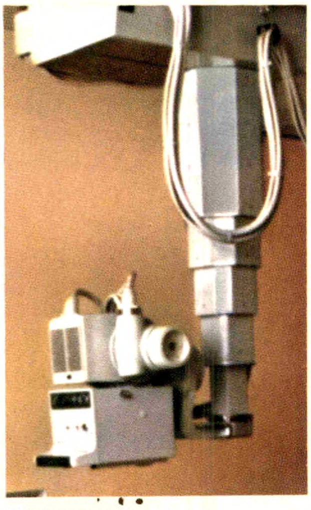

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How to manage data . . . instantly.

To help radiology departments handle large volumes of data, GE has developed two important systems. Maxifile™ system stores data on hundreds of thousands of patients, and any element of the files can be retrieved in seconds. As patients enter the department, previous records can be instantly retrieved. Films can be quickly located. And lost billing is virtually eliminated. Raport® is a computerized radiographic reporting system. As films are read, the radiologist fills out a mark-sense form. In seconds, the Raport system converts the marks into a complete typed report, ready for signature. The combined Raport/Maxfile system gives the radiology department instant data management.

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How to get fast, reliable service.

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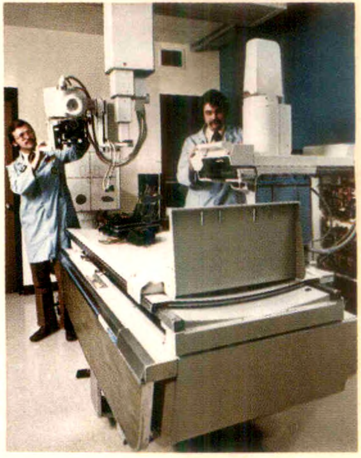

General Electric Medical Systems, Milwaukee, Toronto, Madrid.

GE: leading the way in x-ray.

GENERAL ELECTRIC

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